

=> fil reg; d stat que l10; fil cap1; d que nos l17; fil uspatf; d que nos l25
 FILE IN REGISTRY ENTERED AT 14:57:19 ON 13 DEC 2002
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Property values tagged with IC are from the ZIC/VINITI data file
 provided by InfoChem.

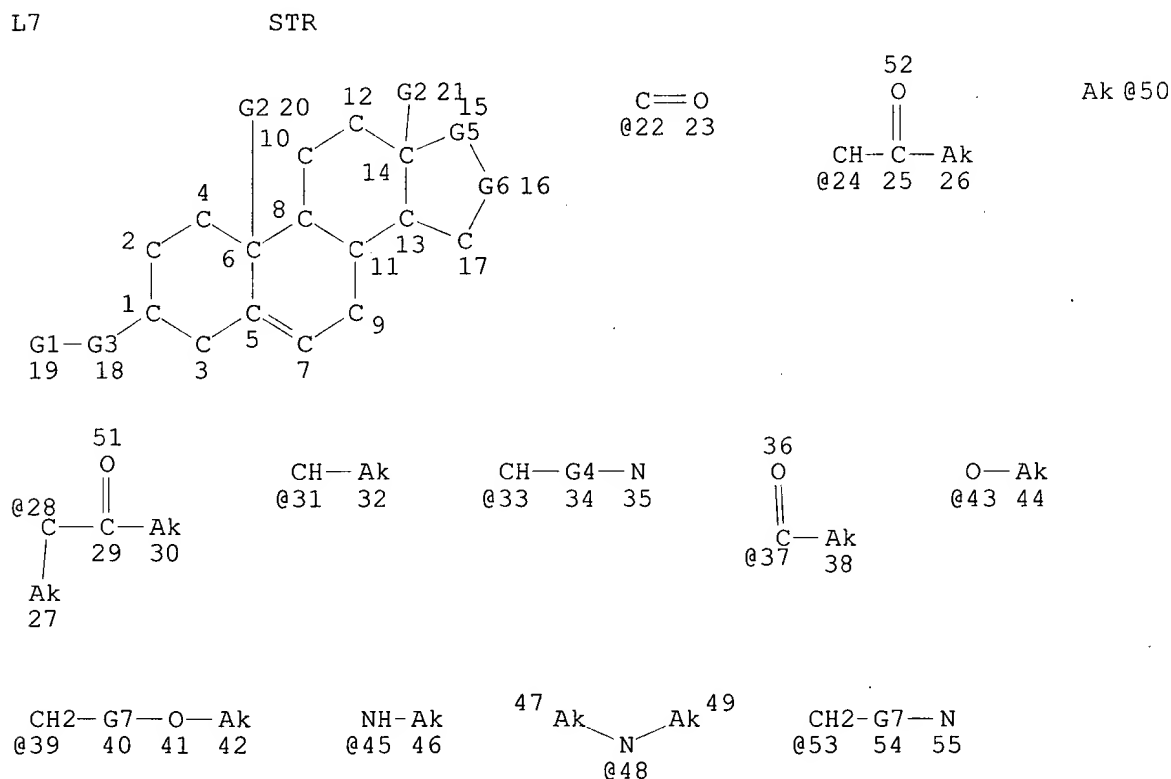
STRUCTURE FILE UPDATES: 12 DEC 2002 HIGHEST RN 476148-76-2
 DICTIONARY FILE UPDATES: 12 DEC 2002 HIGHEST RN 476148-76-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when
 conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP
 PROPERTIES for more information. See STNote 27, Searching Properties
 in the CAS Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>



VAR G1=37/39/43/53/NH2/45/48
 VAR G2=H/50
 VAR G3=O/S
 REP G4=(0-3) CH2
 VAR G5=22/24/28
 VAR G6=CH2/31/33
 REP G7=(0-2) CH2
 NODE ATTRIBUTES:
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CONNECT IS E1 RC AT 27
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CONNECT IS E1 RC AT 49
CONNECT IS E1 RC AT 50
DEFAULT MLEVEL IS ATOM
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GGCAT IS LOC AT 42
GGCAT IS LOC AT 44
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GGCAT IS LOC AT 47
GGCAT IS LOC AT 49
GGCAT IS LOC AT 50
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 55

STEREO ATTRIBUTES: NONE

L9 466 SEA FILE=REGISTRY SSS FUL L7
L10 403 SEA FILE=REGISTRY ABB=ON L9/COMPLETE

FILE 'CAPLUS' ENTERED AT 14:57:19 ON 13 DEC 2002
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FILE COVERS 1907 - 13 Dec 2002 VOL 137 ISS 25
FILE LAST UPDATED: 12 Dec 2002 (20021212/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

L7 STR

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L9          466 SEA FILE=REGISTRY SSS FUL L7
L10         403 SEA FILE=REGISTRY ABB=ON L9/COMPLETE
L11        1224 SEA FILE=CAPLUS ABB=ON L10
L12        6335 SEA FILE=CAPLUS ABB=ON MELANIN#/OBI
L13        1050 SEA FILE=CAPLUS ABB=ON MELANOGEN?/OBI
L14        2592 SEA FILE=CAPLUS ABB=ON SKIN(L) PIGMENT?/OBI
L15        5973 SEA FILE=CAPLUS ABB=ON ENDOSOM?
L16       32023 SEA FILE=CAPLUS ABB=ON LYSOSOM?
L17         18 SEA FILE=CAPLUS ABB=ON L11 AND (L12 OR L13 OR L14 OR L15 OR
          L16)

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FILE 'USPATFULL' ENTERED AT 14:57:20 ON 13 DEC 2002
 CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 12 Dec 2002 (20021212/PD)
 FILE LAST UPDATED: 12 Dec 2002 (20021212/ED)
 HIGHEST GRANTED PATENT NUMBER: US6493878
 HIGHEST APPLICATION PUBLICATION NUMBER: US2002188996
 CA INDEXING IS CURRENT THROUGH 12 Dec 2002 (20021212/UPCA)
 ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 12 Dec 2002 (20021212/PD)
 REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2002
 USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2002

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>>> USPAT2 is now available. USPATFULL contains full text of the    <<<
>>> original, i.e., the earliest published granted patents or      <<<
>>> applications. USPAT2 contains full text of the latest US      <<<
>>> publications, starting in 2001, for the inventions covered in  <<<
>>> USPATFULL. A USPATFULL record contains not only the original  <<<
>>> published document but also a list of any subsequent          <<<
>>> publications. The publication number, patent kind code, and   <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc.                                                       <<<

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>>> USPATFULL and USPAT2 can be accessed and searched together    <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to      <<<
>>> enter this cluster.                                           <<<
>>> Use USPATALL when searching terms such as patent assignees,   <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication.                        <<<

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This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L7          STR
L9          466 SEA FILE=REGISTRY SSS FUL L7
L10         403 SEA FILE=REGISTRY ABB=ON L9/COMPLETE
L18        100 SEA FILE=USPATFULL ABB=ON L10
L19        464 SEA FILE=USPATFULL ABB=ON MELANIN#/TI, IT, AB, CLM
L20         36 SEA FILE=USPATFULL ABB=ON MELANINOGEN?/TI, IT, AB, CLM
L21         73 SEA FILE=USPATFULL ABB=ON MELANOGEN?/TI, IT, AB, CLM
L22        192 SEA FILE=USPATFULL ABB=ON SKIN(2A) PIGMENT?/TI, IT, AB, CLM
L23        241 SEA FILE=USPATFULL ABB=ON LYSOSOM?/TI, IT, AB, CLM
L24         98 SEA FILE=USPATFULL ABB=ON ENDOSOM?/TI, IT, AB, CLM
L25         1 SEA FILE=USPATFULL ABB=ON L18 AND (L19 OR L20 OR L21 OR L22
          OR L23 OR L24)

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=> dup rem 117,125

FILE 'CAPLUS' ENTERED AT 14:57:30 ON 13 DEC 2002
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FILE 'USPATFULL' ENTERED AT 14:57:30 ON 13 DEC 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L17
PROCESSING COMPLETED FOR L25
L60 18 DUP REM L17 L25 (1 DUPLICATE REMOVED)
ANSWERS '1-18' FROM FILE CAPLUS

=> d ibib abs hitstr 160 1-18

L60 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:221159 CAPLUS
DOCUMENT NUMBER: 136:257280
TITLE: Methods and compositions that affect
melanogenesis
INVENTOR(S): Orlow, Seth J.; Hall, Andrea; Manga, Prashiela
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 63 pp., Cont.-in-part of U. S.
Ser. No. 599,487.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002034772	A1	20020321	US 2001-827428	20010406
WO 2002098347	A2	20021212	WO 2002-US11067	20020408
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW			
RW:	AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR			

PRIORITY APPLN. INFO.: US 1999-141563P P 19990629
US 2000-599487 A2 20000623
US 2001-827428 A 20010406

AB The invention provides methods of screening for compds. that affect melanogenesis and the function of P protein in organisms, cells, or cell-free systems. The invention further relates to pharmacol. and cosmetic uses of methods of inhibiting melanogenesis, methods of activating melanogenesis, and compds. and pharmacol. compns. useful for the inhibition or activation of melanogenesis and, therefore, for lightening or darkening the pigmentation of cells and tissue, i.e., skin.

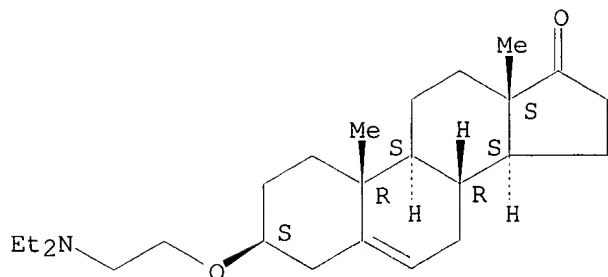
IT 2855-62-1 3039-71-2, U 18666A 5297-33-6
13116-52-4 16321-62-3 23328-05-4
404886-31-3

RL: COS (Cosmetic use); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. that affect **melanogenesis**)

RN 2855-62-1 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, (3.beta.)- (9CI) (CA INDEX NAME)

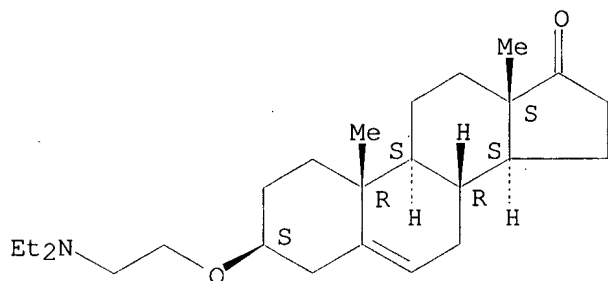
Absolute stereochemistry.



RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride,
(3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

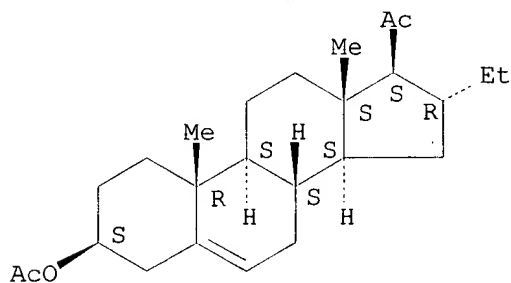


● HCl

RN 5297-33-6 CAPLUS

CN Pregn-5-en-20-one, 3-(acetyloxy)-16-ethyl-, (3.beta.,16.alpha.)- (9CI)
(CA INDEX NAME)

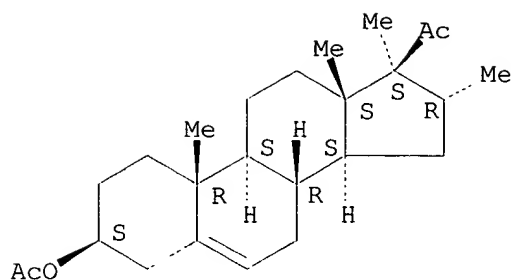
Absolute stereochemistry.



RN 13116-52-4 CAPLUS

CN Pregn-5-en-20-one, 3-(acetyloxy)-16,17-dimethyl-, (3.beta.,16.alpha.)-
(9CI) (CA INDEX NAME)

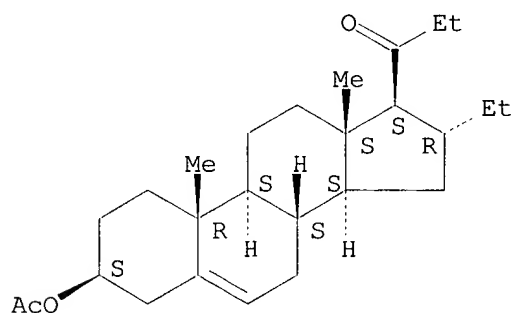
Absolute stereochemistry.



RN 16321-62-3 CAPLUS

CN 1-Propanone, 1-[(3.beta.,16.alpha.,17.beta.)-16-ethyl-3-(acetyloxy)androst-5-en-17-yl]- (9CI) (CA INDEX NAME)

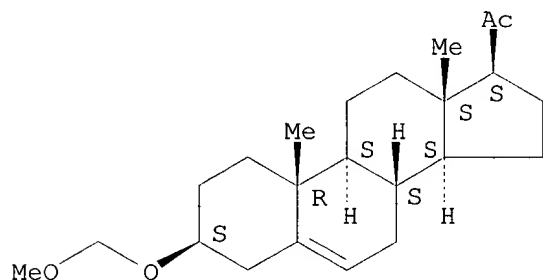
Absolute stereochemistry.



RN 23328-05-4 CAPLUS

CN Pregn-5-en-20-one, 3-(methoxymethoxy)-, (3.beta.)- (9CI) (CA INDEX NAME)

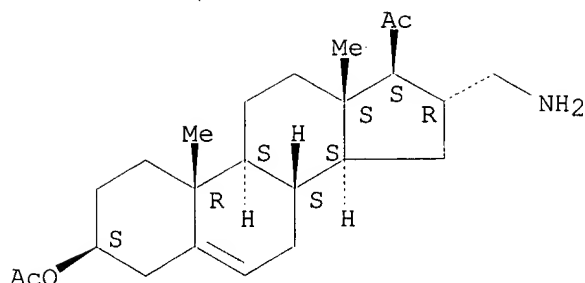
Absolute stereochemistry.



RN 404886-31-3 CAPLUS

CN Pregn-5-en-20-one, 3-(acetyloxy)-16-(aminomethyl)-, (3.beta.,16.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L60 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:71837 CAPLUS

DOCUMENT NUMBER: 136:123406

TITLE: Cosmetic compositions containing
dehydroepiandrosterone or some of its derivatives and
a carotenoid

INVENTOR(S): Breton, Lionel

PATENT ASSIGNEE(S): L'oreal, Fr.

SOURCE: PCT Int. Appl., 23 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002005776	A1	20020124	WO 2001-FR1789	20010608

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

FR 2811569 A1 20020118 FR 2000-9233 20000713

PRIORITY APPLN. INFO.: FR 2000-9233 A 20000713

AB The invention concerns a compn. contg. dehydroepiandrosterone (DHEA) and/or a chem. or biol. precursor or deriv. thereof, characterized in that it further comprises at least a non-provitamin A carotenoid, which can in particular be selected among xanthophyll, lutein and lycopene. The invention also concerns cosmetic and dermatol. uses of said compn., in particular for preventing or treating skin ageing symptoms. A cream contained lycopene 10-4, DHEA 0.1, glycerol stearate 0.1, Polysorbate-60 1, stearic acid 1.4, triethanolamine 0.7, carbomer 0.4, karite butter liq. fraction 12, perhydrosqualene 12, perfume 0.5, preservatives q.s. and water q.s. 100%.

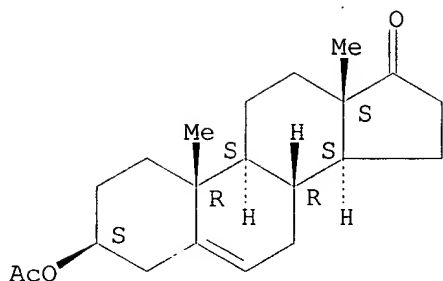
IT 853-23-6 7642-68-4, Dehydroepiandrosterone valerate
23983-43-9

RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(cosmetic compns. contg. dehydroepiandrosterone or some of its derivs.
and carotenoid)

RN 853-23-6 CAPLUS

CN Androst-5-en-17-one, 3-(acetyloxy)-, (3.beta.)- (9CI) (CA INDEX NAME)

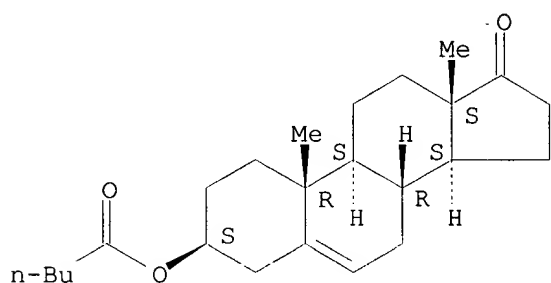
Absolute stereochemistry.



RN 7642-68-4 CAPLUS

CN Androst-5-en-17-one, 3-[(1-oxopentyl)oxy]-, (3.beta.)- (9CI) (CA INDEX NAME)

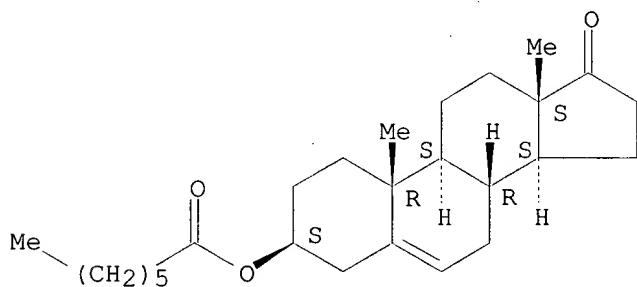
Absolute stereochemistry.



RN 23983-43-9 CAPLUS

CN Androst-5-en-17-one, 3-[(1-oxoheptyl)oxy]-, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:759570 CAPLUS

DOCUMENT NUMBER: 135:308592

TITLE: Cosmetic composition containing a steroid and a 2-alkyl alkanol or ester thereof

INVENTOR(S): Baldo, Francine; Dreher, Susanne

PATENT ASSIGNEE(S): L'Oreal, Fr.

SOURCE: Eur. Pat. Appl., 9 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: French

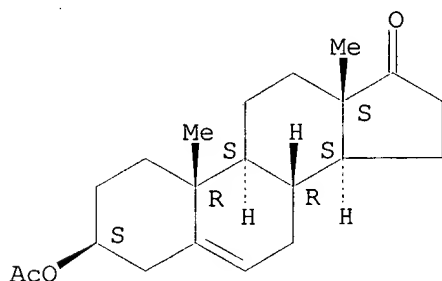
FAMILY ACC. NUM. COUNT: 1

Searched by Barb O'Bryen, STIC 308-4291

PATENT INFORMATION:

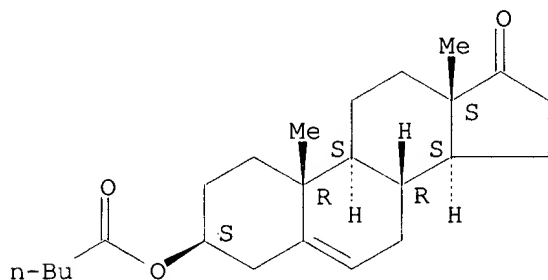
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1145705	A2	20011017	EP 2001-400672	20010314
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
FR 2807323	A1	20011012	FR 2000-4576	20000410
CA 2343426	AA	20011010	CA 2001-2343426	20010409
JP 2001348323	A2	20011218	JP 2001-110585	20010409
US 2001044430	A1	20011122	US 2001-828813	20010410
US 6486147	B2	20021126		
PRIORITY APPLN. INFO.:		FR 2000-4576	A	20000410
OTHER SOURCE(S):		MARPAT 135:308592		
AB	Cosmetic compns. contg. a steroid and a 2-alkyl alkanol or ester thereof are claimed for the prevention or treatment of aging. A cosmetic compn. contained polyglycerol distearate 2, polyethylene glycol mono-stearate 1.35, stearic acid 1, preservatives 1.35, 2-octyldodecanol 5, DHEA 1, C12-15 alc. benzoate 15, neutralizing agents 0.45, propylene glycol 10, gelling agents 0.5, and water q.s. 100%.			
IT	853-23-6 7642-68-4, Dehydroepiandrosterone valerate 23983-43-9, Dehydroepiandrosterone enanthate RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses) (cosmetic compn. contg. steroid and 2-alkyl alkanol or ester thereof)			
RN	853-23-6 CAPLUS			
CN	Androst-5-en-17-one, 3-(acetyloxy)-, (3.beta.)- (9CI) (CA INDEX NAME)			

Absolute stereochemistry.



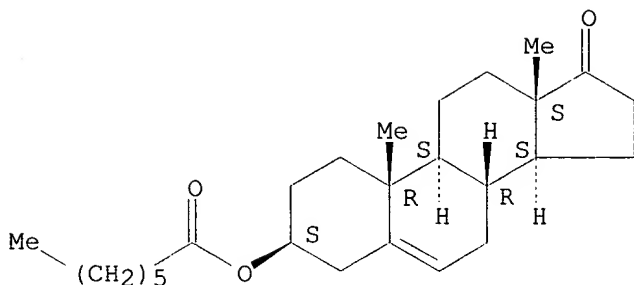
RN 7642-68-4 CAPLUS
 CN Androst-5-en-17-one, 3-[(1-oxopentyl)oxy]-, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 23983-43-9 CAPLUS
 CN Androst-5-en-17-one, 3-[(1-oxoheptyl)oxy]-, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L60 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:412729 CAPLUS

DOCUMENT NUMBER: 133:133759

TITLE: Cholesterol movement in Niemann-Pick type C cells and in cells treated with amphiphiles

AUTHOR(S): Lange, Yvonne; Ye, Jin; Rigney, Mike; Steck, Theodore
CORPORATE SOURCE: Department of Pathology, Rush-Presbyterian-St. Luke's Medical Center, University of Chicago, Chicago, IL, 60637, USA

SOURCE: Journal of Biological Chemistry (2000), 275(23), 17468-17475

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cholesterol accumulates to massive levels in cells from Niemann-Pick type C (NP-C) patients and in cells treated with class 2 amphiphiles that mimic NP-C disease. This behavior has been attributed to the failure of cholesterol released from ingested low density lipoproteins to exit the **lysosomes**. However, the authors now show that the rate of movement of cholesterol from **lysosomes** to plasma membranes in NP-C cells is at least as great as normal, as was also found previously for amphiphile-treated cells. Furthermore, the **lysosomes** in these cells filled with plasma membrane cholesterol in the absence of lipoproteins. In addition, the authors showed that the size of the endoplasmic reticulum cholesterol pool and the set point of the homeostatic sensor of cell cholesterol were approx. normal in NP-C cells. The plasma membrane cholesterol pools in both NP-C and amphiphile-treated cells were also normal. Furthermore, the build up of cholesterol in NP-C **lysosomes** was not a physiological response to cholesterol overload. Rather, it appeared that the accumulation in NP-C **lysosomes** results from an imbalance in the brisk flow of cholesterol among membrane compartments. In related experiments, the authors found that NP-C cells did not respond to class 2 amphiphiles (e.g. trifluoperazine, imipramine, and U18666A); these agents may therefore act directly on the NPC1 protein or on its pathway. Finally, the authors showed that the **lysosomal** cholesterol pool in NP-C cells was substantially and preferentially reduced by incubating cells with the oxysterols, 25-hydroxycholesterol and 7-ketocholesterol; these findings suggest a new pharmacological approach to the treatment of NP-C disease.

IT 3039-71-2, U18666A

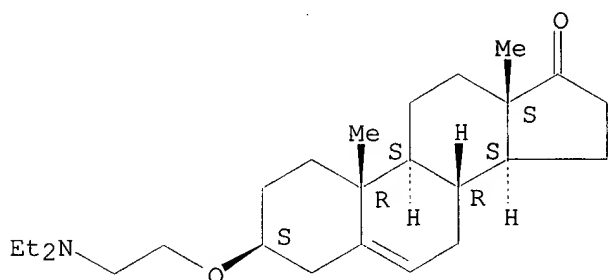
RL: ADV (Adverse effect, including toxicity); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(cholesterol movement in human Niemann-Pick type C cells and in cells treated with amphiphiles as model)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride,
(3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:150925 CAPLUS

DOCUMENT NUMBER: 130:295103

TITLE: Localization of Niemann-Pick C1 protein in astrocytes: implications for neuronal degeneration in Niemann-Pick type C disease

AUTHOR(S): Patel, Shutish C.; Suresh, Sundar; Kumar, Ujendra; Hu, C. Y.; Cooney, Adele; Blanchette-Mackie, E. Joan; Neufeld, Edward B.; Patel, Ramesh C.; Brady, Roscoe O.; Patel, Yogesh C.; Pentchev, Peter G.; Ong, Wei-Yi
CORPORATE SOURCE: Neurobiology Research Laboratory, Veterans Affairs Connecticut Healthcare System, Newington, CT, 06111, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1999), 96(4), 1657-1662
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Niemann-Pick type C disease (NP-C) is an inherited neurovisceral lipid storage disorder characterized by progressive neurodegeneration. Most cases of NP-C result from inactivating mutations of NPC1, a recently identified member of a family of genes encoding membrane-bound proteins contg. putative sterol sensing domains. By using a specific antipeptide antibody to human NPC1, the authors have here investigated the cellular and subcellular localization and regulation of NPC1. By light and electron microscopic immunocytochem. of monkey brain, NPC1 was expressed predominantly in perisynaptic astrocytic glial processes. At a subcellular level, NPC1 localized to vesicles with the morphol. characteristics of **lysosomes** and to sites near the plasma membrane. Anal. of the temporal and spatial pattern of neurodegeneration in the NP-C mouse, a spontaneous mutant model of human NP-C, by amino-cupric-silver staining, showed that the terminal fields of axons and dendrites are the earliest sites of degeneration that occur well before the appearance of a neurol. phenotype. Western blots of cultured human fibroblasts and monkey brain homogenates revealed NPC1 as a 165-kDa protein. NPC1 levels in cultured fibroblasts were unchanged by incubation with low d. lipoproteins or oxysterols but were increased 2- to 3-fold by the drugs progesterone and U-18666A, which block cholesterol transport out

of lysosomes, and by the lysosomotropic agent NH_4Cl .

These studies show that NPC1 in brain is predominantly a glial protein present in astrocytic processes closely assocd. with nerve terminals, the earliest site of degeneration in NP-C. Given the vesicular localization of NPC1 and its proposed role in mediating retroendocytic trafficking of cholesterol and other **lysosomal** cargo, these results suggest that disruption of NPC1-mediated vesicular trafficking in astrocytes may be linked to neuronal degeneration in NP-C.

IT 3039-71-2, U-18666A

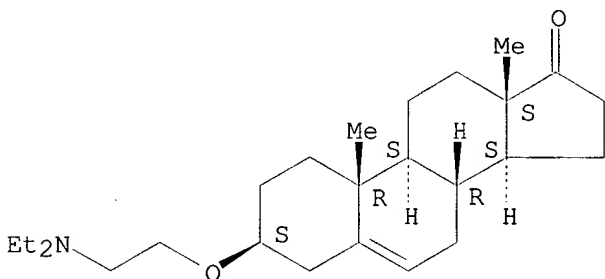
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(Niemann-Pick C1 protein in fibroblasts of humans response to cholesterol transport-blockers progesterone and U-18666A and **lysosomotropic** NH₄Cl)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride,
(3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:105930 CAPLUS

DOCUMENT NUMBER: 130:279626

TITLE: U18666A inhibits intracellular cholesterol transport
and neurotransmitter release in human neuroblastoma
cells

AUTHOR(S): Sparrow, Susan M.; Carter, Jodi M.; Ridgway, Neale D.;
Cook, Harold W.; Byers, David M.

CORPORATE SOURCE: Atlantic Research Centre, Departments of Pediatrics
and Biochemistry, Dalhousie University, Halifax, NS,
B3H 4H7, Can.

SOURCE: Neurochemical Research (1999), 24(1), 69-77

CODEN: NEREDZ; ISSN: 0364-3190

PUBLISHER: Plenum Publishing Corp.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To det. if neurochem. function might be impaired in cell models with altered cholesterol balance, we studied the effects of U18666A (3- β -(2-diethyl-amino)ethoxy)androst-5-en-17-one) on intracellular cholesterol metab. in three human neuroblastoma cell lines (SK-N-SH, SK-N-MC, and SH-SY5Y). U18666A (1 μ M) completely inhibited low d. lipoprotein (LDL)-stimulated cholesterol esterification in SK-N-SH cells, while cholesterol esterification stimulated by

25-hydroxycholesterol or bacterial sphingomyelinase was unaffected or partially inhibited, resp. U18666A also blocked LDL-stimulated downregulation of LDL receptor and caused **lysosomal** accumulation of cholesterol as measured by filipin staining. U18666A treatment for 18 h resulted in 70% inhibition of K⁺-evoked norepinephrine release in phorbol ester-differentiated SH-SY5Y cells, while release stimulated by the calcium ionophore A23187 was only slightly affected. These results suggest that U18666A may preferentially block a voltage-regulated Ca²⁺ channel involved in norepinephrine release and that alterations in neurotransmitter secretion might be a feature of disorders such as Niemann-Pick Type C, in which intracellular cholesterol transport and distribution are impaired.

IT 3039-71-2, U18666A

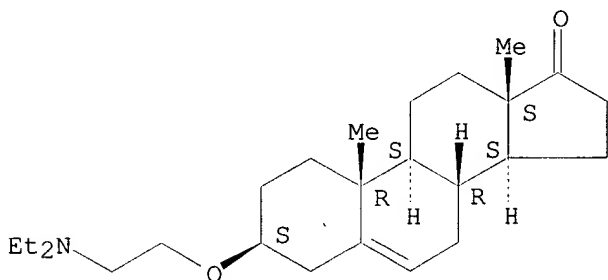
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(U18666A inhibits intracellular cholesterol transport and neurotransmitter release in human neuroblastoma cells)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:573480 CAPLUS

DOCUMENT NUMBER: 131:321114

TITLE: Niemann-Pick C1 Is a Late **Endosome**-Resident Protein That Transiently Associates with **Lysosomes** and the Trans-Golgi Network

AUTHOR(S): Higgins, Maureen E.; Davies, Joanna P.; Chen, Fannie W.; Ioannou, Yiannis A.

CORPORATE SOURCE: Department of Human Genetics, Mount Sinai School of Medicine, New York, NY, 10029, USA

SOURCE: Molecular Genetics and Metabolism (1999), 68(1), 1-13 CODEN: MGMEFF; ISSN: 1096-7192

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Niemann-Pick type C (NPC) disease is a severe cell lipidosis characterized by the accumulation of unesterified cholesterol in the **endosomal** /**lysosomal** system. Recently the primary disease-causing gene, NPC1, was identified, but few clues regarding its potential function(s) could be derived from its predicted amino acid sequence. Therefore, efforts were directed at characterizing the subcellular location of the

NPC1 protein. Initial studies with a FLAG-tagged NPC1 cDNA demonstrated that NPC1 is a glycoprotein that assoc. with the membranes of a population of cytoplasmic vesicles. Immunofluorescence microscopy using anti-NPC1 polyclonal antibodies confirmed this anal. Double-label immunofluorescence microscopy and subcellular fractionation studies indicated that NPC1 assoc. predominantly with late **endosomes** (Rab9 GTPase-pos. vesicles) and, to a lesser extent, with **lysosomes** and the trans-Golgi network. When cholesterol egress from **lysosomes** was blocked by treatment of cells with U18666A, the NPC1 location shifted from late **endosomes** to the trans-Golgi network and **lysosomes**. Subcellular fractionation of liver homogenates from U18666A-treated mice confirmed these observations. These data suggest that U18666A may inhibit the retrograde transport of NPC1 from **lysosomes** to late **endosomes** for subsequent transfer to the trans-Golgi network. (c) 1999 Academic Press.

IT 3039-71-2, U18666A

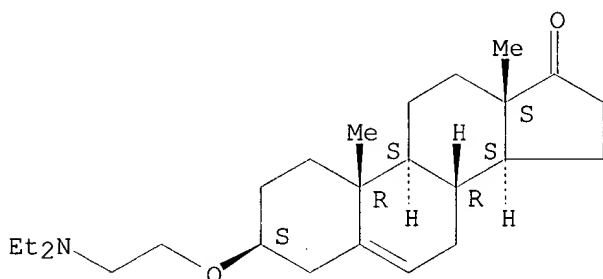
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(cholesterol egress from **lysosomes** is blocked by treatment of human cells with U18666A, also shifting NPC1 location from late **endosomes** to trans-Golgi network and **lysosomes**)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:515842 CAPLUS

DOCUMENT NUMBER: 129:214809

TITLE: Circulation of cholesterol between **lysosomes** and the plasma membrane

AUTHOR(S): Lange, Yvonne; Ye, Jin; Steck, Theodore L.

CORPORATE SOURCE: Departments of Pathology and Biochemistry, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, 60612, USA

SOURCE: Journal of Biological Chemistry (1998), 273(30), 18915-18922

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

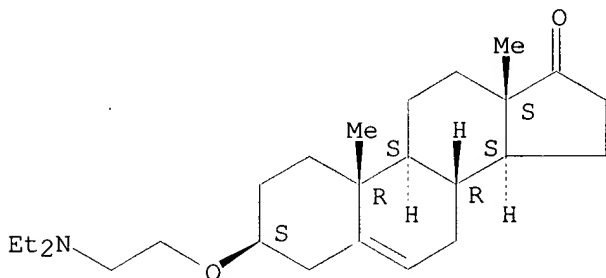
LANGUAGE: English

AB The cholesterol in the **lysosomes** of cultured human fibroblasts

was detd. to constitute .apprx.6% of the cell total. This pool was enlarged by as much as 10-fold in Niemann-Pick type C cells. Certain amphiphiles (e.g. U18666A, progesterone, and imipramine) caused **lysosomal** cholesterol to increase to similarly high levels at a rate of .apprx.0.8% of cell cholesterol/h. **Lysosomal** cholesterol accumulated even in the absence of exogenous lipoproteins. Furthermore, nearly all of the **lysosomal** cholesterol in both of the perturbed systems was shown to be derived from the plasma membrane. Oxysterols known to alter cholesterol movement and homeostasis blocked **lysosomal** cholesterol accretion in amphiphile-treated cells, suggesting that this process is regulated physiol. Treating cells with amphiphiles slightly reduced the efflux of cholesterol from **lysosomes** and slightly increased the influx from the plasma membrane, causing the **lysosomal** cholesterol compartment to double in size in .apprx.15 h. After more prolonged amphiphile treatments, a population of buoyant **lysosomes** appeared that exchanged cholesterol with the plasma membrane completely but slowly. Niemann-Pick type C **lysosomes** were similarly buoyant and sluggish. We conclude that cholesterol circulates bi-directionally between the plasma membrane and **lysosomes**. The massive accumulation of **lysosomal** cholesterol in the perturbed cells does not appear to reflect disabled **lysosomal** transport but rather the formation of **lysosomes** modified for lipid storage, i.e. lamellar bodies.

IT 3039-71-2, U18666A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(circulation of cholesterol between **lysosomes** and the plasma membrane)
RN 3039-71-2 CAPLUS
CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:443682 CAPLUS
DOCUMENT NUMBER: 127:174214
TITLE: The fate of cholesterol exiting **lysosomes**
AUTHOR(S): Lange, Yvonne; Ye, Jin; Chin, Janet
CORPORATE SOURCE: Department of Pathology and Biochemistry,
Rush-Presbyterian-St. Luke's Medical Center, Chicago,
IL, 60612, USA
SOURCE: Journal of Biological Chemistry (1997), 272(27),

Searched by Barb O'Bryen, STIC 308-4291

17018-17022

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER:

American Society for Biochemistry and Molecular
Biology

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB Cholesterol released from ingested low d. lipoproteins in **lysosomes** moves both to the plasma membrane and to the endoplasmic reticulum (ER) where it is re-esterified. Whether cholesterol can move directly from **lysosomes** to ER or first must traverse the plasma membrane has not been established. To examine this question, the endocytic pathway of rat hepatoma cells was loaded at 18.degree.C with low d. lipoproteins (LDL) labeled with [3H]cholesteryl linoleate, and the label then was chased at 37.degree.C. The hydrolysis of the accumulated ester proceeded linearly for several hours. Almost all of the released [3H]cholesterol moved to the plasma membrane rapidly and without a discernable lag. In contrast, the re-esterification in the ER of the released [3H]cholesterol showed a characteristic lag of 0.5-1 h. These data are inconsistent with direct cholesterol transfer from **lysosomes** to ER; rather, they suggest movement through the plasma membrane. Furthermore, it was found that progesterone, imipramine and 3-.beta.-[2-(diethylamino)ethoxy]androst-5-en-17-one (U18666A) strongly inhibited the re-esterification of **lysosomal** cholesterol in the ER. However, contrary to previous reports, they did not block transfer of [3H]cholesterol from **lysosomes** to the cell surface. Therefore, the site of action of these agents was not at the **lysosomes**. It is suggested instead that their known ability to block cholesterol movement from the plasma membrane to the ER accounts for the inhibition of **lysosomal** cholesterol esterification. These findings are consistent with the hypothesis that cholesterol released from **lysosomes** passes through the plasma membrane on its way to the ER rather than proceeding there directly. As a result, ingested cholesterol is subject to the same homeostatic regulation as the bulk of cell cholesterol, which is located in the plasma membrane.

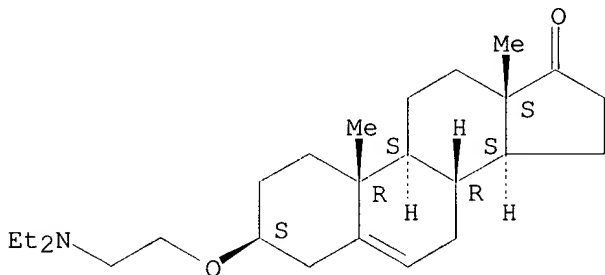
IT 3039-71-2, U18666A

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect on **lysosomal** cholesterol re-esterification in ER)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride,
(3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L60 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2002 ACS

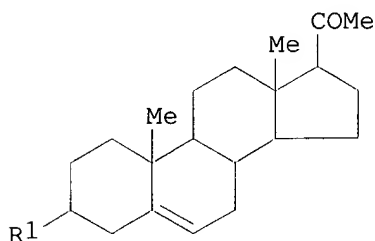
ACCESSION NUMBER: 1997:144312 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT NUMBER: 126:190762
 TITLE: **Melanin** formation inhibitors containing pregnenolones
 INVENTOR(S): Hashizume, Ron; Ootsuki, Yoshikazu; Kamoda, Hironobu
 PATENT ASSIGNEE(S): Adobansuto Sukin Risaachi Kenk, Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 08337528	A2	19961224	JP 1995-148623	19950615

OTHER SOURCE(S): MARPAT 126:190762
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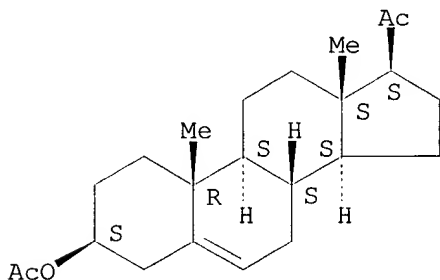


AB The melanin formation inhibitors contain pregnenolones I (R1 = C1-18 carboxyl, OH, OSO3H). Pregnenolone (at 25 .mu.M) showed significant whitening effect on cultured HM3KO cells (human skin melanoma cells). Formulation examples of ointments, skin lotions, and cosmetic packs are given.

IT **1778-02-5**, Pregnenolone acetate
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
 (pregnenolones as **melanin** formation inhibitors for skin-lightening)

RN 1778-02-5 CAPLUS
 CN Pregn-5-en-20-one, 3-(acetyloxy)-, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



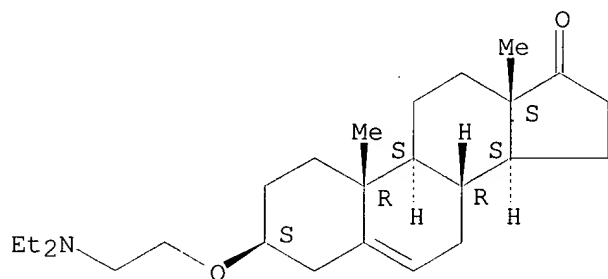
L60 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1996:457190 CAPLUS
 DOCUMENT NUMBER: 125:164266

TITLE: Quantitative analysis of hydrophobic amine inhibition of intracellular cholesterol transport
AUTHOR(S): Underwood, Kathryn W.; Andemariam, Biree; McWilliams, Gail L.; Liscum, Laura
CORPORATE SOURCE: Dep. of Physiology, Tufts Univ. Sch. of Med., Boston, MA, 02111, USA
SOURCE: Journal of Lipid Research (1996), 37(7), 1556-1568
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB U18666A and imipramine are hydrophobic amines that inhibit intracellular cholesterol transport pathways. In this study, we conducted dose-response curves for each of the cholesterol transport pathways. Our analyses indicate that hydrophobic amine inhibition of LDL-stimulated cholesterol esterification is much more sensitive to inhibition than either the combined bulk movement of cholesterol from **lysosomes** to the plasma membrane and from the plasma membrane to the endoplasmic reticulum. Hydrophobic amines must inhibit a previously uncharacterized pathway from **lysosomes** to the endoplasmic reticulum or a signaling event that activates acyl CoA:cholesterol acyltransferase. Possible mechanisms for U18666A action were evaluated. The function of p-glycoprotein, which has been implicated in cholesterol transport, was unaffected by U18666A. We have evidence for a specific membrane U18666A binding site, which we hypothesize is involved in the plasma membrane to endoplasmic reticulum cholesterol transport pathway. Identification of the binding site and mechanism of hydrophobic amine action may provide information essential for understanding intracellular cholesterol transport.

IT 3039-71-2, U18666A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(hydrophobic amine inhibition of intracellular cholesterol transport)
RN 3039-71-2 CAPLUS
CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L60 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:677299 CAPLUS
DOCUMENT NUMBER: 121:277299
TITLE: Cholesterol homeostasis. Modulation by amphiphiles
AUTHOR(S): Lange, Yvonne; Steck, Theodore
CORPORATE SOURCE: Departments Pathology Biochemistry,
Rush-Presbyterian-St. Luke's Medical Center, Chicago,
IL, 60612, USA

Searched by Barb O'Bryen, STIC 308-4291

SOURCE: Journal of Biological Chemistry (1994), 269(47), 29371-4
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

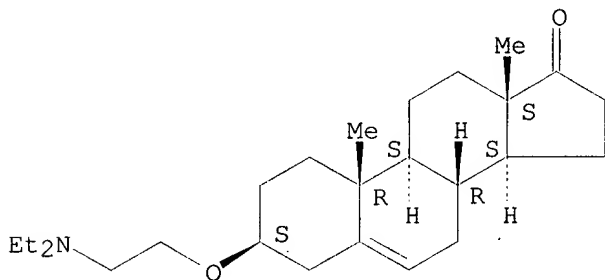
AB Diverse amphiphiles act on cellular cholesterol metab. as if signaling regulatory sites. One class (oxysterols) mimics the homeostatic effects of excess cell cholesterol, inhibiting cholesterol biosynthesis and stimulating plasma membrane cholesterol esterification. A second class of amphiphiles has effects precisely opposite to the oxysterols, i.e. they immediately inhibit plasma membrane cholesterol esterification and progressively induce 3-hydroxy-3-methylglutaryl-CoA reductase activity and cholesterol biosynthesis. This second class of agents includes steroids, hydrophobic amines, phenothiazines, ionophores, colchicine, cytochalasins, and lysophosphatides, most of which interact with P-glycoproteins. These data support a general hypothesis, given below, describing cellular cholesterol homeostasis. Proteins regulating sterol metab. are embedded in intracellular membranes where their activities are governed by the local level of cholesterol. Excess plasma membrane and **lysosomal** cholesterol circulates through those intracellular membranes and sets the homeostatic activities therein. The two classes of agents mentioned above affect cholesterol homeostasis by increasing or decreasing, resp., the ambient level of cholesterol at the sites of regulation.

IT 3039-71-2, U18666A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cholesterol esterification by hepatocytes response to)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L60 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:499250 CAPLUS

DOCUMENT NUMBER: 121:99250

TITLE: Effects of the glucosphingolipid synthesis inhibitor, PDMP, on **lysosomes** in cultured cells

AUTHOR(S): Rosenwald, Anne G.; Pagano, Richard E.

CORPORATE SOURCE: Dep. Embryol., Carnegie Inst. Washington, Baltimore, MD, 21210, USA

SOURCE: Journal of Lipid Research (1994), 35(7), 1232-40
CODEN: JLPRAW; ISSN: 0022-2275

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The glucosphingolipid synthesis inhibitor, 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) has a wide range of effects on cell physiolo. and morphol. Here, the authors studied the effects of high concns. of PDMP on cells in culture and found that fluorescent analogs of PDMP targeted to the **lysosomes** of Chinese hamster ovary (CHO) cells. Overnight incubation of the cells in the presence of drug induced enlargement ("vacuolization") of the **lysosomes**. PDMP was toxic at high concns. (>30.mu.m); this finding was used to select CHO cells that exhibited increased resistance to PDMP (PDMPR cells). The PDMPR cells were .apprx.2-fold more resistant to PDMP than the parental cells (CHO-P). PDMPR cells were resistant to a no. of other drugs that are also lipophilic and possess a titrable amino group. The multidrug resistance exhibited by the PDMPR cells was distinct from that obsd. in cells (MDR cells) that overproduce the plasma membrane drug pump, P-glycoprotein. In addn., MDR cells were extremely sensitive to PDMP.

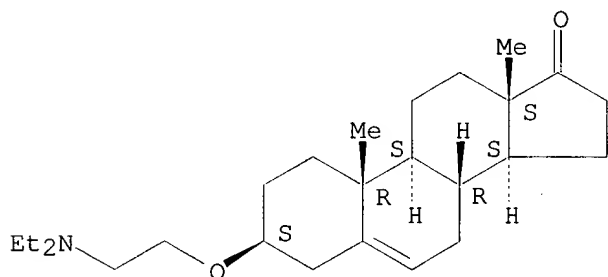
IT 3039-71-2, U18666A

RL: BIOL (Biological study)
(resistance to, in cells resistant to glucosphingolipid synthesis inhibitor PDMP)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride,
(3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L60 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:500066 CAPLUS

DOCUMENT NUMBER: 121:100066

TITLE: Structure-specific inhibition of **lysosomal**
cholesterol transport in macrophages by various
steroids

AUTHOR(S): Aikawa, Kazuhiro; Furuchi, Takemitsu; Fujimoto,
Yoshinori; Arai, Hiroyuki; Inoue, Keizo

CORPORATE SOURCE: Department of Health Chemistry, Faculty of
Pharmaceutical Sciences, The University of Tokyo,
Tokyo 113, Hongo 7-3-1, Bunkyo-ku, Japan

SOURCE: Biochimica et Biophysica Acta (1994), 1213(2), 127-34
CODEN: BBACAQ; ISSN: 0006-3002

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cultured mouse peritoneal macrophages effectively take up and metabolize liposomes contg. phosphatidylserine and cholesterol, resulting in massive accumulation of cholesteryl esters and triacylglycerols in their cytoplasm (Nishikawa, K. et al, 1990). With this system, various steroid derivs. were assessed as to their ability to inhibit the cholesteryl ester

formation from endocytosed cholesterol in macrophages. Among the steroids tested, one group of steroids having an oxo group at the C17 or C20 position, such as androstenedione, dehydroisoandrosterone, progesterone and pregnenolone, completely inhibited cholesteryl ester formation at 10 μ M. Another group of steroids having a hydroxy group at the C17 position, such as testosterone and androstenediol, had a lesser effect; complete inhibition of cholesteryl ester formation was achieved with 100 μ M or more. The mechanism underlying the inhibition by the former class of steroids was further studied. These steroids did not block the uptake or **lysosomal** hydrolysis of liposomes, nor esterification of fatty acyl chains into triacylglycerols. Moreover, dehydroisoandrosterone and pregnenolone, both of which possess a hydroxy group at the C3 position, had essentially no effect on 25-hydroxycholesterol-stimulated esterification of endogenous cellular cholesterol. Androstenedione and progesterone, which possess an oxo group at the C3 position, had a mild inhibitory effect on the esterification of endogenous cholesterol. Upon incubation with a steroid having an oxo group at the C17 or C20 position, free cholesterol taken up by macrophages was accumulated in phagolysosomes, as judged from cytochem. study with filipin-cholesterol staining. These results indicate that a series of structurally-related steroids characterized by the presence of an oxo group at the C17 or C20 position inhibit cholesteryl ester formation in macrophages through blocking the intracellular transport of endocytosed cholesterol from **lysosomes** to endoplasmic reticulum.

IT 3039-71-2, U 18666A

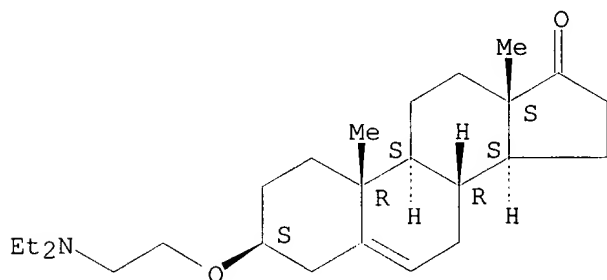
RL: BIOL (Biological study)

(cholesterol intracellular transport and cholesterol esterification inhibition by, in macrophage, mol. structure in relation to)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride, (3. β .)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L60 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:532612 CAPLUS

DOCUMENT NUMBER: 115:132612

TITLE: Characterization of Chinese hamster ovary cells that are resistant to 3- β -[2-(diethylamino)ethoxy]androst-5-en-17-one inhibition of low density lipoprotein-derived cholesterol metabolism

AUTHOR(S): Liscum, Laura; Collins, Gail J.

CORPORATE SOURCE: Sch. Med., Tufts Univ., Boston, MA, 02111, USA

SOURCE: Journal of Biological Chemistry (1991), 266(25), 16599-606

CODEN: JBCHA3; ISSN: 0021-9258

Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pharmacol. agent U18666A (3-.beta.-[2-(diethylamino)ethoxy]androst-5-en-17-one inhibits the intracellular transport of low-d. lipoprotein (LDL)-derived cholesterol in Chinese hamster ovary (CHO) cells. LDL-derived cholesterol accumulates in the **lysosomes** of U18666A-treated cells causing delayed LDL-mediated regulation of cellular cholesterol metab. and impaired movement of LDL-derived cholesterol to other cell membranes. As a result of impaired LDL-derived cholesterol transport, LDL-dependent growth of CHO cells is also inhibited by U18666A. By selecting for cell growth in the presence of U18666A, the authors have identified a CHO cell line, designated U18R, that is resistant to U18666A-inhibition of LDL-derived cholesterol trafficking. When compared to parental CHO cells, U18R cells are relatively resistant to U18666A inhibition of LDL-derived cholesterol transport as well as LDL-mediated regulation of cellular cholesterol metab. In cell fusion expts., the U18666A resistance obsd. in U18R cells displays a dominant phenotype. Identification of the U18666A-resistant factor may provide important insights toward the understanding of intracellular LDL-derived cholesterol regulation and trafficking.

IT 3039-71-2, U18666A

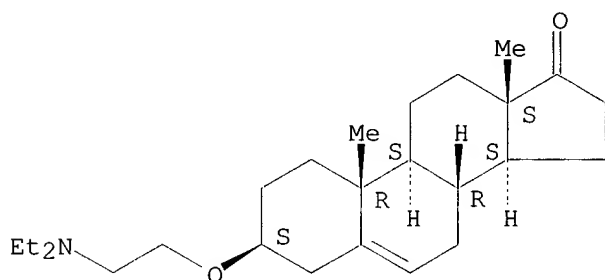
RL: BIOL (Biological study)

(low-d. lipoprotein-derived cholesterol metab. of CHO cells inhibition by, resistance to)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L60 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1990:509101 CAPLUS

DOCUMENT NUMBER: 113:109101

TITLE: Pharmacological inhibition of the intracellular transport of low-density lipoprotein-derived cholesterol in Chinese hamster ovary cells

AUTHOR(S): Liscum, Laura

CORPORATE SOURCE: Sch. Med., Tufts Univ., Boston, MA, 02111, USA

SOURCE: Biochimica et Biophysica Acta (1990), 1045(1), 40-8

CODEN: BBACAQ; ISSN: 0006-3002

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mammalian cells, cultured in the presence of serum lipoproteins, acquire cholesterol necessary for growth from the uptake and **lysosomal** hydrolysis of low-d. lipoproteins (LDL). The mechanism(s) of intracellular transport of LDL-derived cholesterol from **lysosomes**

to other cellular sites is unknown. In this study, various pharmacol. agents were assessed for their ability to inhibit the movement of LDL-cholesterol from **lysosomes** to the plasma membrane. The only pharmacol. agent tested in these expts. that specifically inhibited LDL-cholesterol movement was U18666A. Ketoconazole impaired the intracellular transport of LDL-cholesterol; however, ketoconazole also had a general effect on cholesterol movement, since it impeded the desorption of endogenously synthesized cholesterol into the medium. Other drugs that affected cholesterol movement appeared to be nonspecific. Cholesterol transport from **lysosomes** to plasma membranes was not significantly altered by agents that affect **lysosomal** function or cytoskeletal organization, as well as energy poisons and cycloheximide.

IT 3039-71-2, U18666A

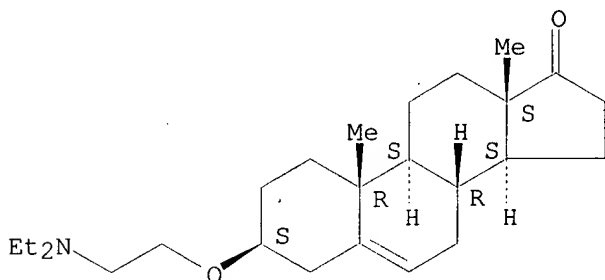
RL: BIOL (Biological study)

(low-d. lipoprotein-derived cholesterol transport from **lysosomes** to cell membrane response to)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L60 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1989:490648 CAPLUS

DOCUMENT NUMBER: 111:90648

TITLE: The intracellular transport of low density lipoprotein-derived cholesterol is inhibited in Chinese hamster ovary cells cultured with 3-.beta.-[2-(diethylamino)ethoxy]androst-5-en-17-one

AUTHOR(S): Liscum, Laura; Faust, Jerry R.

CORPORATE SOURCE: Sch. Med., Tufts Univ., Boston, MA, 02111, USA

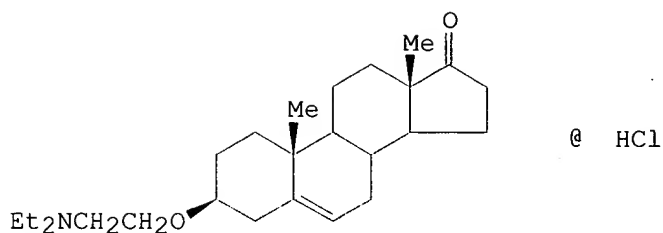
SOURCE: Journal of Biological Chemistry (1989), 264(20), 11796-806

CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



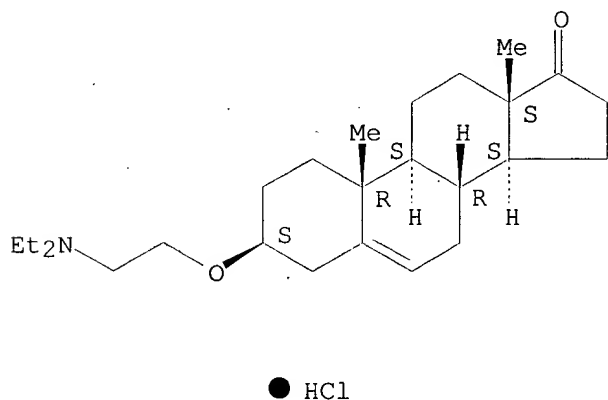
AB In mammalian cells, low-d. lipoprotein (LDL) is bound, internalized, and delivered to **lysosomes** where LDL-cholesteryl esters are hydrolyzed to unesterified cholesterol. The mechanisms of intracellular transport of LDL-cholesterol from **lysosomes** to other cellular sites and LDL-mediated regulation of cellular cholesterol metab. are unknown. A pharmacol. agent, U18666A (I; 3-.beta.-[2-(diethylamino)ethoxy]androst-5-en-17-one), which impairs the intracellular transport of LDL-derived cholesterol in cultured Chinese hamster ovary (CHO) cells, is described. U18666A blocks the ability of LDL-derived cholesterol to stimulate cholesterol esterification, and to suppress 3-hydroxy-3-methylglutaryl-CoA reductase and LDL receptor activities. However, U18666A does not impair 25-hydroxycholesterol-mediated regulation of these processes. In addn., U18666A impedes the ability of LDL-derived cholesterol to support the growth of CHO cells. However, U18666A has only moderate effects on growth supported by nonlipoprotein cholesterol. LDL binding, internalization, and **lysosomal** hydrolysis of LDL-cholesteryl esters are not affected by the presence of U18666A. Anal. of intracellular cholesterol transport reveals that LDL-derived cholesterol accumulates in the **lysosomes** of U18666A-treated CHO cells, which results in impaired movement of LDL-derived cholesterol to other cell membranes.

IT 3039-71-2, U 18666A
 RL: BIOL (Biological study)
 (low-d. lipoprotein-derived cholesterol intracellular transport inhibition by, in ovary cells in culture)

RN 3039-71-2 CAPLUS

CN Androst-5-en-17-one, 3-[2-(diethylamino)ethoxy]-, hydrochloride, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L60 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1965:464794 CAPLUS
 DOCUMENT NUMBER: 63:64794

ORIGINAL REFERENCE NO.: 63:11948h,11949a-b

TITLE: The action of steroids and Streptolysin S on the permeability of phospholipid structures to cations

AUTHOR(S): Bangham, A. D.; Standish, M. M.; Weissmann, G.

CORPORATE SOURCE: Agr. Res. Council Inst. Animal Physiol., Cambridge, UK

SOURCE: J. Mol. Biol. (1965), 13(1), 253-9

DOCUMENT TYPE: Journal

LANGUAGE: English

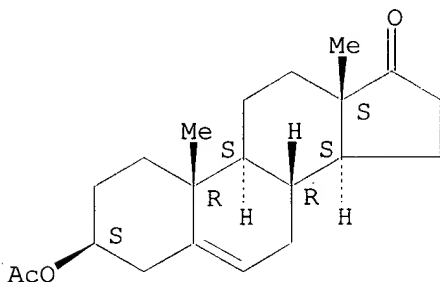
AB The properties of aq. suspensions of phospholipids, composed of concentric bimol. lamellae, are similar to many of the important permeability properties of biol. membranes of mitochondria or erythrocytes and esp. the myelin-figure form of **lysosomes**. When exposed to diethylstilbestrol, etiocholanolone, deoxycorticosterone, progesterone, pregnanolone, pregnanolone acetate, corticosterone, androsterone, 5-androsten-3.beta.-ol-17-one acetate, and Streptolysin S, the permeability of these model membrane systems was altered in directions similar to biol. membranes (Na⁺, K⁺, and acid phosphatase were released). Allopregnanolone and, to a greater extent, cortisol, cortisone acetate, cortisone, and chloroquine reduced the leakage of these systems. These studies support the concept that these aq. suspensions of phospholipids are valuable models and that the membrane action of biol. active steroids results from their direct interaction with lipids, independent of polysaccharide, protein, or active cell metabolism. 47 references.

IT 853-23-6, Androst-5-en-17-one, 3.beta.-hydroxy-, acetate (prepn. of)

RN 853-23-6 CAPLUS

CN Androst-5-en-17-one, 3-(acetyloxy)-, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> fil embase; d que 112; d que 115
FILE 'EMBASE' ENTERED AT 16:02:58 ON 17 DEC 2002
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FILE COVERS 1974 TO 12 Dec 2002 (20021212/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

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L1 1161 SEA FILE=EMBASE ABB=ON MELANOGENESIS/CT
L6 3453 SEA FILE=EMBASE ABB=ON MELANIN/CT
L7 2756 SEA FILE=EMBASE ABB=ON SKIN PIGMENTATION+NT/CT
L8 10154 SEA FILE=EMBASE ABB=ON LYSOSOME/CT
L9 3183 SEA FILE=EMBASE ABB=ON ENDOSOME/CT
L10 57 SEA FILE=EMBASE ABB=ON ENDOLYSOSOM?
L12 5 SEA FILE=EMBASE ABB=ON (L1 OR L6 OR L7) AND ((L8 AND L9) OR L10)

L13 1266 SEA FILE=EMBASE ABB=ON LYSOSOM?(5A)ENDOSOM?
L14 98683 SEA FILE=EMBASE ABB=ON DRUG EFFECT/CT
L15 12 SEA FILE=EMBASE ABB=ON L13 AND L14

=> s 112 or 115
L82 17 L12 OR L15

=> fil capl; d que 149;d que 156
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FILE COVERS 1907 - 17 Dec 2002 VOL 137 ISS 25
FILE LAST UPDATED: 16 Dec 2002 (20021216/ED)

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CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

L44 (2592)SEA FILE=CAPLUS ABB=ON SKIN(L)PIGMENT?/OBI
L45 (5973)SEA FILE=CAPLUS ABB=ON ENDOSOM?

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L46 (      32023)SEA FILE=CAPLUS ABB=ON  LYSOSOM?
L47 (      5415)SEA FILE=CAPLUS ABB=ON  SKIN(2A)CELL#/OBI
L48 (      1392)SEA FILE=CAPLUS ABB=ON  (L44 OR L47) AND PHARMAC?/SC,SX
L49          6 SEA FILE=CAPLUS ABB=ON  L48 AND (L45 OR L46)

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L50 (      6335)SEA FILE=CAPLUS ABB=ON  MELANIN#/OBI
L51 (      1050)SEA FILE=CAPLUS ABB=ON  MELANOGEN?/OBI
L52 (      5973)SEA FILE=CAPLUS ABB=ON  ENDOSOM?
L53 (      32023)SEA FILE=CAPLUS ABB=ON  LYSOSOM?
L54 (        59)SEA FILE=CAPLUS ABB=ON  ENDOLYSOSOM?
L55 (      897)SEA FILE=CAPLUS ABB=ON  (L50 OR L51) AND PHARMAC?/SC,SX
L56          0 SEA FILE=CAPLUS ABB=ON  L55 AND ((L52 AND L53) OR L54)

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=> fil medl; d que 175; d que 166; s 175 or 166
 FILE 'MEDLINE' ENTERED AT 16:03:02 ON 17 DEC 2002

FILE LAST UPDATED: 14 DEC 2002 (20021214/UP). FILE COVERS 1958 TO DATE.

On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See <http://www.nlm.nih.gov/mesh/summ2003.html> for a description on changes.

If you received SDI results from MEDLINE on October 8, 2002, these may have included old POPLINE data and in some cases duplicate abstracts. For further information on this situation, please visit NLM at: http://www.nlm.nih.gov/pubs/techbull/so02/so02_popline.html

To correct this problem, CAS will remove the POPLINE records from the MEDLINE file and process the SDI run dated October 8, 2002 again.

Customers who received SDI results via email or hard copy prints on October 8, 2002 will not be charged for this SDI run. If you received your update online and displayed answers, you may request a credit by contacting the CAS Help Desk at 1-800-848-6533 in North America or 614-447-3698 worldwide, or via email to help@cas.org

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L67 (      117752)SEA FILE=MEDLINE ABB=ON  SKIN+NT/CT
L68 (        8433)SEA FILE=MEDLINE ABB=ON  PIGMENTATION+NT/CT
L69 (        2672)SEA FILE=MEDLINE ABB=ON  SKIN PIGMENTATION/CT
L70 (        5425)SEA FILE=MEDLINE ABB=ON  MELANINS/CT
L71 (       37017)SEA FILE=MEDLINE ABB=ON  LYSOSOM?
L72 (        6113)SEA FILE=MEDLINE ABB=ON  ENDOSOM?
L73 (         54)SEA FILE=MEDLINE ABB=ON  ENDOLYSOSOM?
L74 (       14155)SEA FILE=MEDLINE ABB=ON  (L71 OR L72 OR L73) AND (PD OR PK OR
      DT OR TU OR AD)/CT
L75          7 SEA FILE=MEDLINE ABB=ON  L74 AND ((L67 AND (L70 OR L68)) OR
      L69)

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Subheadings
 PD = pharmacology
 PK = pharmacokinetics
 DT = drug therapy
 TU = therapeutic use
 AD = administration & dosage

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L57 (      22508)SEA FILE=MEDLINE ABB=ON  LYSOSOMES+NT/CT
L58 (      2151)SEA FILE=MEDLINE ABB=ON  ENDOSOMES/CT
L59 (     117752)SEA FILE=MEDLINE ABB=ON  SKIN+NT/CT
L60 (        8433)SEA FILE=MEDLINE ABB=ON  PIGMENTATION+NT/CT

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L61 (2672)SEA FILE=MEDLINE ABB=ON SKIN PIGMENTATION/CT
 L62 (5425)SEA FILE=MEDLINE ABB=ON MELANINS/CT
 L63 (20)SEA FILE=MEDLINE ABB=ON (L57 OR L58) AND ((L59 AND (L62 OR L60)) OR L61)
 L64 (661)SEA FILE=MEDLINE ABB=ON (L57 OR L58) AND (L59 OR L60 OR L61 OR L62)
 L65 (176)SEA FILE=MEDLINE ABB=ON L64 AND (PD OR PK OR DT OR TU OR AD)/CT
 L66 3 SEA FILE=MEDLINE ABB=ON L63 AND L65

L83 7 L75 OR L66

=> fil wpids; d que l81
 FILE 'WPIDS' ENTERED AT 16:03:05 ON 17 DEC 2002
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FILE LAST UPDATED: 16 DEC 2002 <20021216/UP>
 MOST RECENT DERWENT UPDATE: 200281 <200281/DW>
 DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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L76 (2592)SEA FILE=WPIDS ABB=ON SKIN(3A)(PIGMENT? OR CELL#)
 L77 (1576)SEA FILE=WPIDS ABB=ON MELANOGEN? OR MELANIN#
 L78 (167)SEA FILE=WPIDS ABB=ON ENDOSOM?
 L79 (459)SEA FILE=WPIDS ABB=ON LYSOSOM?
 L80 (2)SEA FILE=WPIDS ABB=ON ENDOLYSOSOM?
 L81 4 SEA FILE=WPIDS ABB=ON (L76 OR L77) AND (L78 OR L79 OR L80)

=> dup rem l83,l49,l82,l81
 FILE 'MEDLINE' ENTERED AT 16:03:24 ON 17 DEC 2002

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PROCESSING COMPLETED FOR L83
 PROCESSING COMPLETED FOR L49
 PROCESSING COMPLETED FOR L82
 PROCESSING COMPLETED FOR L81

L84 34 DUP REM L83 L49 L82 L81 (0 DUPLICATES REMOVED)
 ANSWERS '1-7' FROM FILE MEDLINE

ANSWERS '8-13' FROM FILE CAPLUS
ANSWERS '14-30' FROM FILE EMBASE
ANSWERS '31-34' FROM FILE WPIDS

=> d ibib ab 1-34

L84 ANSWER 1 OF 34 MEDLINE
ACCESSION NUMBER: 2001108905 MEDLINE
DOCUMENT NUMBER: 20580353 PubMed ID: 11139343
TITLE: Regulation of the catalytic activity of preexisting tyrosinase in black and Caucasian human melanocyte cell cultures.
AUTHOR: Fuller B B; Spaulding D T; Smith D R
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, 73104, USA.. bryan-fuller@ouhsc.edu
SOURCE: EXPERIMENTAL CELL RESEARCH, (2001 Jan 15) 262 (2) 197-208. Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

AB The activity of tyrosinase, the rate-limiting enzyme for melanin synthesis, is higher in Black skin melanocytes than in melanocytes derived from Caucasian skin. This variation in enzyme activity is not due to differences in tyrosinase abundance or tyrosinase gene activity, but, rather, is due to differences in the catalytic activity of preexisting tyrosinase. In melanocytes, tyrosinase is localized to the membrane of melanosomes and in Caucasian melanocytes the melanosome-bound enzyme is largely inactive. Conversely, in melanosomes of Black melanocytes, tyrosinase has high catalytic activity. Treatment of Caucasian melanocytes with the **lysosomotropic** compound ammonium chloride or with the ionophores nigericin and monensin results in a rapid and pronounced increase in tyrosinase activity. This increase occurs without any change in tyrosinase abundance, indicating that these compounds are increasing the catalytic activity of preexisting enzyme. Inhibition of the vacuolar proton pump V-ATPase by treatment of Caucasian melanocytes with bafilomycin also increases tyrosinase activity. In contrast to the 10-fold increase in tyrosinase observed in Caucasian melanocytes, neither ammonium chloride, monensin, nigericin, nor bafilomycin is able to increase the already high level of tyrosinase activity present in melanosomes of melanocytes derived from Black skin. Finally, staining of Caucasian melanocytes with the fluorescent weak base acridine orange shows that melanosomes of Caucasian, but not Black, melanocytes are acidic organelles. These data support a model for racial pigmentation that is based on differences in melanosome pH in Black and Caucasian skin types. The models suggests that melanosomes of Caucasian melanocytes are acidic, while those of Black individuals are more neutral. Since tyrosinase is inactive in an acid environment, the enzyme is largely inactive in Caucasian melanosomes but fully active in Black melanosomes.
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L84 ANSWER 2 OF 34 MEDLINE
ACCESSION NUMBER: 2001412103 MEDLINE
DOCUMENT NUMBER: 21354456 PubMed ID: 11461115
TITLE: Melanosomal pH controls rate of melanogenesis, eumelanin/phaeomelanin ratio and melanosome maturation in melanocytes and melanoma cells.
AUTHOR: Ancans J; Tobin D J; Hoogduijn M J; Smit N P; Wakamatsu K;

Thody A J
CORPORATE SOURCE: Department of Biomedical Sciences, University of Bradford,
Bradford, BD7 1DP, United Kingdom.
SOURCE: EXPERIMENTAL CELL RESEARCH, (2001 Aug 1) 268 (1) 26-35.
Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB The skin pigment melanin is produced in melanocytes in highly specialized organelles known as melanosomes. Melanosomes are related to the organelles of the **endosomal/lysosomal** pathway and can have a low internal pH. In the present study we have shown that melanin synthesis in human pigment cell lysates is maximal at pH 6.8. We therefore investigated the role of intramelanosomal pH as a possible control mechanism for melanogenesis. To do this we examined the effect of neutralizing melanosomal pH on tyrosinase activity and melanogenesis in 11 human melanocyte cultures and in 3 melanoma lines. All melanocyte cultures (9 of 9) from Caucasian skin as well as two melanoma cell lines with comparable melanogenic activity showed rapid (within 24 h) increases in melanogenesis in response to neutralization of melanosomal pH. Chemical analysis of total melanin indicated a preferential increase in eumelanin production. Electron microscopy revealed an accumulation of melanin and increased maturation of melanosomes in response to pH neutralization. In summary, our findings show that: (i) near neutral melanosomal pH is optimal for human tyrosinase activity and melanogenesis; (ii) melanin production in Caucasian melanocytes is suppressed by low melanosomal pH; (iii) the ratio of eumelanin/phaeomelanin production and maturation rate of melanosomes can be regulated by melanosomal pH. We conclude that melanosomal pH is an essential factor which regulates multiple stages of melanin production. Furthermore, since we have recently identified that pink locus product (P protein) mediates neutralization of melanosomal pH, we propose that P protein is a key control point for skin pigmentation. We would further propose that the wide variations in both constitutive and facultative skin pigmentation seen in the human population could be associated with the high degree of P-locus polymorphism.
Copyright 2001 Academic Press.

L84 ANSWER 3 OF 34 MEDLINE
ACCESSION NUMBER: 84152938 MEDLINE
DOCUMENT NUMBER: 84152938 PubMed ID: 6703775
TITLE: A semiquantitative light and electron microscopic analysis
of histopathologic changes in photochemotherapy-induced
freckles.
AUTHOR: Kanerva L; Niemi K M; Lauharanta J
SOURCE: ARCHIVES OF DERMATOLOGICAL RESEARCH, (1984) 276 (1) 2-11.
Journal code: 8000462. ISSN: 0340-3696.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198404
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19840413

AB Photochemotherapy(PUVA)-induced freckles were found in 25 patients (41%) who had received more than 1,000 J/cm2 of PUVA. The patients had been treated with PUVA for more than 2 years, with more than 150 exposures before PUVA lentigines appeared on the thighs, the upper arm, the

mid-lower arm, the waist, and the buttocks. The histopathology of these freckles was analyzed by light and electron microscopy. Light microscopy showed an increased amount of pigment and melanophages and increased numbers and size of melanocytes. The keratinocytes often displayed atypical features such as enlarged nuclei, giant size, or fibrillar degeneration. Homogenization of the papillary dermis was observed in 11 patients. The activation of melanocytes was confirmed electron microscopically, and pathological features such as large amounts of lipid droplets and **lysosome**-melanosome complexes within the melanocytes were seen. The Langerhans cells were mostly normal, whereas the keratinocytes showed cytolytic changes, fibrillar degeneration, and vacuolization. A close follow-up of patients with prolonged PUVA treatment is recommended.

L84 ANSWER 4 OF 34 MEDLINE

ACCESSION NUMBER: 83267003 MEDLINE

DOCUMENT NUMBER: 83267003 PubMed ID: 6409969

TITLE: Selective aberration and pigment loss in melanosomes of malignant melanoma cells in vitro by glycosylation inhibitors: premelanosomes as glycoprotein.

AUTHOR: Mishima Y; Imokawa G

SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1983 Aug) 81 (2) 106-14.

Journal code: 0426720. ISSN: 0022-202X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198309

ENTRY DATE: Entered STN: 19900319

Last Updated on STN: 19900319

Entered Medline: 19830909

AB We have found that glucosamine (1 mg/ml) or tunicamycin (0.2-0.4 micrograms/ml), specific inhibitors of lipid carrier-dependent glycosylation of protein, when added to cultured B-16 melanoma cells produce a marked loss of pigmentation, accompanied by distinctive biochemical as well as ultrastructural aberrations in their melanogenic compartments. Electron microscopic analysis shows that these newly induced unpigmented cells form uniquely altered melanosomes containing little or no melanin, although their population is not substantially reduced. Within the melanogenic compartments, selective aberration of melanosomes is seen, that is, deformity, bulging, and segregation of their interior membrane, as well as the intramelanosomal formation of irregularly concentric lamellar structure. No apparent structural deformity of Golgi apparatus, Golgi-associated endoplasmic reticulum of **lysosome** (GERL), and coated vesicles has been observed. Further, no substantial alteration is seen in mitochondria or other cellular structures. Quantitative analysis of altered and nonaltered melanosomes has revealed that the ratio of altered premelanosomes to the total number increases to 44% in glucosamine-treated cells and to 99.5% in tunicamycin-treated cells. Compared to 13% in the control. Electron microscopic dopa reaction has also revealed that these altered melanosomes seem to exhibit a weakly positive or a negative dopa reaction in both glucosamine- and tunicamycin-treated melanoma cells although a number of dopa-positive altered melanosomes are still seen. However, GERL and coated vesicles show no apparent decrease in dopa reaction. It may be concluded that glycoprotein synthesis is integral to the formation of normal melanosomes and to their specific melanizing function, which could be impaired by inhibition of the synthesis of asparagin-linked mannose-containing sugar chains. This results in retrogressive changes in the premelanosomal tyrosinase during its maturation process.

L84 ANSWER 5 OF 34 MEDLINE

ACCESSION NUMBER: 76006507 MEDLINE
DOCUMENT NUMBER: 76006507 PubMed ID: 808573
TITLE: **Lysosomes** and the skin.
AUTHOR: Lazarus G S; Hatcher V B; Levine N
SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1975 Sep) 65 (3)
259-71. Ref: 133
Journal code: 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 197512
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19990129
Entered Medline: 19751204

L84 ANSWER 6 OF 34 MEDLINE
ACCESSION NUMBER: 74111834 MEDLINE
DOCUMENT NUMBER: 74111834 PubMed ID: 4521831
TITLE: Epidermal **lysosome** and the degradation of
melanosomes.
AUTHOR: Saito N; Seiji M
SOURCE: ACTA DERMATO-VENEREOLOGICA. SUPPLEMENTUM, (1973) 73 69-73.
Journal code: 0370311. ISSN: 0365-8341.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197405
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19970203
Entered Medline: 19740502

L84 ANSWER 7 OF 34 MEDLINE
ACCESSION NUMBER: 71238853 MEDLINE
DOCUMENT NUMBER: 71238853 PubMed ID: 4997370
TITLE: Regulation of tyrosinase activity in mouse melanoma and
skin by changes in melanosomal membrane permeability.
AUTHOR: Van Woert M H; Korb F; Prasad K N
SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1971 May) 56 (5)
343-8.
Journal code: 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 197109
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19900101
Entered Medline: 19710901

L84 ANSWER 8 OF 34 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:221159 CAPLUS
DOCUMENT NUMBER: 136:257280
TITLE: Methods and compositions that affect melanogenesis
INVENTOR(S): Orlow, Seth J.; Hall, Andrea; Manga, Prashiela
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 63 pp., Cont.-in-part of U. S.
Ser. No. 599,487.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002034772	A1	20020321	US 2001-827428	20010406
WO 2002098347	A2	20021212	WO 2002-US11067	20020408
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				

PRIORITY APPLN. INFO.: US 1999-141563P P 19990629
 US 2000-599487 A2 20000623
 US 2001-827428 A 20010406

AB The invention provides methods of screening for compds. that affect melanogenesis and the function of P protein in organisms, cells, or cell-free systems. The invention further relates to pharmacol. and cosmetic uses of methods of inhibiting melanogenesis, methods of activating melanogenesis, and compds. and pharmacol. compns. useful for the inhibition or activation of melanogenesis and, therefore, for lightening or darkening the pigmentation of cells and tissue, i.e., skin.

L84 ANSWER 9 OF 34 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:312016 CAPLUS

DOCUMENT NUMBER: 136:319375

TITLE: Method and composition for treating cancer using cellular organelle crystallizing agents

INVENTOR(S): Kong, Qingzhong

PATENT ASSIGNEE(S): USA

SOURCE: U.S., 19 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6376525	B1	20020423	US 2000-663559	20000915
WO 2001082780	A2	20011108	WO 2001-US13730	20010427
WO 2001082780	A3	20020124		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001057383	A5	20011112	AU 2001-57383	20010427
US 2002143042	A1	20021003	US 2002-96156	20020311

PRIORITY APPLN. INFO.: CN 2000-111092 A 20000429
 US 2000-663559 A 20000915
 US 2000-687342 A 20001012
 CN 2000-129316 A 20001113

AB This invention provides a method for treating cancer in mammals through cellular-organelle-crystn.-induced-death (herein defined as "Cocid"), a

method for treating cancer using cellular organelle and/or cytoskeleton crystg. agents (e.g. tetrazolium salts and their derivs.), pharmaceutical compns. contg. a therapeutically effective amt. of organelle and/or cytoskeleton crystg. agents, and compns. contg. organelle and/or cytoskeleton crystg. agents in combination with a pharmaceutically acceptable carrier, diluent or excipient. The crystg. agents with or without a pharmaceutically acceptable carrier, diluent or excipient, are used in combination with surgery and/or non-surgical anti-tumor treatments.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 10 OF 34 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:662859 CAPLUS

DOCUMENT NUMBER: 134:33070

TITLE: Novel hepatotrophic prodrugs of the antiviral nucleoside 9-(2-phosphonylmethoxyethyl)adenine with improved pharmacokinetics and antiviral activity

AUTHOR(S): Biessen, E. A. L.; Valentijn, A. R. P. M.; de Vruhe, R. L. A.; van de Bilt, E.; Sliedregt, L. A. J. M.; Prince, P.; Bijsterbosch, M. K.; van Boom, J. H.; van der Marel, G. A.; Abrahms, P. J.; van Berkel, T. J. C.

CORPORATE SOURCE: Division of Biopharmaceutics, LACDR, LIC Leiden University, Leiden, Neth.

SOURCE: FASEB Journal (2000), 14(12), 1784-1792

CODEN: FAJOEC; ISSN: 0892-6638

PUBLISHER: Federation of American Societies for Experimental Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The device of new hepatotrophic pro-drugs of the antiviral nucleoside 9-(2-phosphonylmethoxyethyl)adenine (PMEA) with specificity for the asialoglycoprotein receptor on parenchymal liver cells is described. PMEA was conjugated to bi- and trivalent cluster glycosides (K(GN)2 and K2(GN)3, resp.) with nanomolar affinity for the asialoglycoprotein receptor. The liver uptake of the PMEA prodrugs was more than 10-fold higher than that of the parent drug (52.+-0.6% and 62.+-0.3% vs. 4.8.+-0.7% of the injected dose for PMEA) and could be attributed for 90% to parenchymal cells. Accumulation of the PMEA prodrugs in extrahepatic tissue (e.g., kidney, skin) was substantially reduced. The ratio of parenchymal liver cell-to-kidney uptake - a measure of the prodrugs therapeutic window - was increased from 0.058 .+- 0.01 for PMEA to 1.86 .+- 0.57 for K(GN)2-PMEA and even 2.69 .+- 0.24 for K2(GN)3-PMEA. Apparently both glycosides have a similar capacity to redirect (antiviral) drugs to the liver. After cellular uptake, both PMEA prodrugs were converted into the parent drug, PMEA, during acidification of the lysosomal milieu (t1/2.approx.100 min), and the released PMEA was rapidly translocated into the cytosol. The antiviral activity of the prodrugs in vitro was dramatically enhanced as compared to the parent drug (5- and 52-fold for K(GN)2-PMEA and K2(GN)3-PMEA, resp.). Given the 15-fold enhanced liver uptake of the prodrugs, we anticipate that the potency in vivo will be similarly increased. We conclude that PMEA prodrugs have been developed with greatly improved pharmacokinetics and therapeutic activity against viral infections that implicate the liver parenchyma (e.g., HBV). In addn., the significance of the above prodrug concept also extends to drugs that intervene in other liver disorders such as cholestasis and dyslipidemia.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 11 OF 34 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:444160 CAPLUS

DOCUMENT NUMBER: 133:317015

TITLE: Modulation of skin reactions: a general overview
AUTHOR(S): Kydonieus, Agis F.; Wille, John J.
CORPORATE SOURCE: Samos Pharmaceuticals, LLC, Kendall Park, NJ, USA
SOURCE: Biochemical Modulation of Skin Reactions (2000),
205-221. Editor(s): Kydonieus, Agis F.; Wille, John
J. CRC Press LLC: Boca Raton, Fla.
CODEN: 69ACIH

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

AB A review with 92 refs. The mechanisms of irritant, as well as allergic contact dermatitis are still not totally understood, although a lot of progress has been made during the last few years as demonstrated by the advances presented in Chapters 7 through 13 of this vol. It is not, therefore, surprising that the patent literature reviewed in this chapter involves, to a large degree, inventions based on observation and trial and error approaches. The methodol. and results presented in most cases would not pass peer review. The quality of the patent literature has improved in the last few years, as the science of immunol. is making progress in understanding the mechanisms involved in these processes. The sections on Metabolic Modulators, Ion Channel Modulators, and Mast Cell Degranulators are based on the latest understanding of science which is still evolving. Alza, Bristol-Myers, and L'Oreal appear to be in the forefront in trying to apply the latest scientific breakthroughs to the delivery of drugs and cosmetics to skin with reduced skin reactions. It is reasonable to assume that, as the science improves, so will the approaches of abrogating contact dermatitis.

REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 12 OF 34 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1981:41484 CAPLUS

DOCUMENT NUMBER: 94:41484

TITLE: Reversible cellular damage by dimethyl sulfoxide reflected by release of marker enzymes for intracellular fractions

AUTHOR(S): Volden, Gunnar; Haugen, Hans Fredrik; Skrede, Sverre

CORPORATE SOURCE: Dep. Dermatol., Rikshosp., Oslo, Norway

SOURCE: Archives of Dermatological Research (1980), 269(2), 147-51

CODEN: ADREDL; ISSN: 0340-3696

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Irritative human skin reactions were induced by DMSO [67-68-5]. Suction blisters were raised on these areas within 1.5 h after their induction, and simultaneously on normal skin. The activities of marker enzymes for subcellular fractions in the suction blisters were detd. In suction blisters raised on the DMSO-induced wheals, significantly higher values of the cytosol enzyme lactate dehydrogenase [9001-60-9] and also some higher values of the **lysosomal** marker .alpha.-mannosidase [9025-42-7] were found than in blisters produced on normal skin. Membrane-bound marker enzymes for subcellular fractions were not elevated. Since the skin is macroscopically completely normal 24 h after application of DMSO, it appears that the induction of membrane damage and release of intracellular enzymes does not necessarily lead to cellular necrosis.

L84 ANSWER 13 OF 34 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1973:12225 CAPLUS

DOCUMENT NUMBER: 78:12225

TITLE: Amiodarone pigmentation. Electron microscopic study
AUTHOR(S): Geerts, M. L.

CORPORATE SOURCE: Dep. Dermatol., Univ. Ghent, Ghent, Belg.

SOURCE: Arch. Belg. Dermatol. Syphiligr. (1971), 27(4), 339-51
CODEN: ABBSAY

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prolonged treatment of persons with Amiodarone (I) [1951-25-3] provoked in some of them a blue gray coloration of the face and the back of the hands. Histol. and histochem. studies indicated a lipofuscin pigment in the macrophages in the vicinity of the superficial dermis capillaries. In 1 person the skin contained increased levels of iodine [7553-56-2]. Electron microscopy revealed the pigment granules as **lysosomes** with various morphols.

L84 ANSWER 14 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002427641 EMBASE

TITLE: Azithromycin, a lysosomotropic antibiotic, has distinct effects on fluid-phase and receptor-mediated endocytosis, but does not impair phagocytosis in J774 macrophages.

AUTHOR: Tyteca D.; Van Der Smissen P.; Mettlen M.; Van Bambeke F.; Tulkens P.M.; Mingeot-Leclercq M.-P.; Courtoy P.J.

CORPORATE SOURCE: P.J. Courtoy, Unite de Biologie Cellulaire, Universite Catholique de Louvain, C. D. Intl. I. Cell./Molec. Pathol., UCL 7541 Avenue Hippocrate 75, B-1200 Brussels, Belgium. courtoy@cell.ucl.ac.be

SOURCE: Experimental Cell Research, (2003) 281/1 (86-100).
Refs: 91

ISSN: 0014-4827 CODEN: ECREAL

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Pretreatment of J774 mouse macrophages by the dicationic macrolide antibiotic, azithromycin (AZ), selectively inhibited fluid-phase endocytosis of horseradish peroxidase and lucifer yellow, but not phagocytosis of latex beads. AZ delayed sequestration of receptor-bound transferrin and peroxidase-anti-peroxidase immune complexes into cell-surface endocytic pits and vesicles, but did not slow down the subsequent rate of receptor-mediated endocytosis. AZ down-regulated cell surface transferrin receptors, but not Fc.gamma. receptors, by causing a major delay in the accessibility of internalized transferrin receptors to the recycling route, without slowing down subsequent efflux, resulting in redistribution of the surface pool to an intracellular pool. Acidotropic accumulation of AZ was associated with an extensive vacuolation of late **endosomes/lysosomes**, and these compartments became unaccessible to horseradish peroxidase and immune complexes, but not to latex beads. The inhibitory profile of AZ cannot be solely accounted for by vacuolation and interference with acidification. AZ may help in dissecting various steps of the endocytic apparatus such as lateral mobility of receptors at the plasma membrane, formation of clathrin-independent endocytic vesicles, orientation of transferrin receptors into the recycling route, and fusogenicity with lysosomes.
.COPYRGT. 2002 Elsevier Science (USA).

L84 ANSWER 15 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002324187 EMBASE

TITLE: Tyrosinase and tyrosinase-related protein 1 require Rab7 for their intracellular transport.

AUTHOR: Hirotsaki K.; Yamashita T.; Wada I.; Jin H.-Y.; Jimbow K.

CORPORATE SOURCE: Dr. K. Jimbow, Department of Dermatology, Sapporo Med. Univ. Sch. of Medicine, South 1, West 16, Chuo-ku, Sapporo 060, Japan. jimbow@sapmed.ac.jp

SOURCE: Journal of Investigative Dermatology, (2002) 119/2 (475-480).
Refs: 50

ISSN: 0022-202X CODEN: JIDEAE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We have recently identified the association of Rab7 in melanosome biogenesis and proposed that Rab7 is involved in the transport of tyrosinase-related protein 1 from the trans-Golgi network to melanosomes, possibly passing through late-endosome-delineated compartments. In order to further investigate the requirement of Rab7-containing compartments for vesicular transport of tyrosinase family proteins, we expressed tyrosinase and tyrosinase-related protein by recombinant adenovirus and analyzed their localization in human amelanotic melanoma cells (SK-mel-24) in the presence or absence of a dominant-negative mutant of Rab7 (Rab7N125I). Co-infection of the recombinant adenoviruses carrying tyrosinase (Ad-HT) and TRP-1 (Ad-TRP-1) resulted in the enhancement of tyrosinase activity and melanin production compared to a single infection of Ad-HT. In the Ad-HT-infected SK-mel-24 cells many of the newly synthesized tyrosinase proteins were colocalized in lysosomal lgp85-positive granules of the entire cytoplasm, whereas in the presence of Rab7N125I the colocalization of tyrosinase and lgp85 proteins was decreased markedly in the distal area of the cytoplasm. In the Ad-TRP-1-infected SK-mel-24 cells, TRP-1, which is reported to be present exclusively in melanosomes, was detected throughout the cytoplasm, but not colocalized in prelysosomal (early endosomal) EEA-1 granules. In the presence of Rab7N125I, however, TRP-1 was retained in the EEA-1-positive granules. Our findings indicate that the dominant-negative mutant of Rab7 impairs vesicular transport of tyrosinase and TRP-1, suggesting that the transport of these melanogenic proteins from the trans-Golgi network to maturing melanosomes requires passage through endosome-delineated compartments.

L84 ANSWER 16 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002138035 EMBASE

TITLE: The dark side of lysosome-related organelles:
Specialization of the endocytic pathway for melanosome biogenesis.

AUTHOR: Raposo G.; Marks M.S.

CORPORATE SOURCE: G. Raposo, UMR-144, Institut Curie, CNRS, Paris Cedex 75005, France. graposo@curie.fr

SOURCE: Traffic, (2002) 3/4 (237-248).

Refs: 91

ISSN: 1398-9219 CODEN: TRAFFA

COUNTRY: Denmark

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Melanosomes are lysosome-related organelles within which melanin pigments are synthesized and stored in melanocytes and retinal pigment epithelial cells. Early ultrastructural studies of pigment cells revealed that melanosomes consist of a complex series of organelles; more recently, these structures have been correlated with cargo constituents. By studying the fate of melanosomal and endosomal cargo in melanocytic cells, the effects of disease-related mutations on melanosomal morphology, and the genes affected by these mutations, we are beginning to gain novel insights into the biogenesis of these complex organelles and their relationship to the endocytic pathway. These insights demonstrate how specialized cells integrate unique and ubiquitous molecular mechanisms in subverting the endosomal system to generate cell-type specific structures and their associated functions. Further dissection of the melanosomal system will

likely shed light not only on the biogenesis of lysosome-related organelles but also on general aspects of vesicular transport in the endosomal system.

L84 ANSWER 17 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002093197 EMBASE
TITLE: Melanosomal pH, pink locus protein and their roles in melanogenesis [3].
AUTHOR: Brilliant M.; Gardner J.
CORPORATE SOURCE: M. Brilliant, Department of Pediatrics, Univ. of Arizona School of Medicine, Tucson, AZ, United States
SOURCE: Journal of Investigative Dermatology, (2001) 117/2 (386-387).
Refs: 20
ISSN: 0022-202X CODEN: JIDEAE
COUNTRY: United States
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 002 Physiology
013 Dermatology and Venereology
029 Clinical Biochemistry
LANGUAGE: English

L84 ANSWER 18 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001145178 EMBASE
TITLE: Inhibitory effect of (+)-catechin on the growth of influenza A/PR/8 virus in MDCK cells.
AUTHOR: Mantani N.; Imanishi N.; Kawamata H.; Terasawa K.; Ochiai H.
CORPORATE SOURCE: H. Ochiai, Department of Human Science, Faculty of Medicine, Toyama Medical/Pharmaceutical Univ., Sugitani 2630, Toyama 930-0194, Japan. ochiai@ms.toyama-mpu.ac.jp
SOURCE: Planta Medica, (2001) 67/3 (240-243).
Refs: 14
ISSN: 0032-0943 CODEN: PLMEAA
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We investigated whether (+)-catechin, a building block of tannins contained in the extract of Ephedrae herba (EHext), exerts an inhibitory effect on the acidification of intracellular compartments such as **endosomes** and **lysosomes** (referred to as ELS), and thereby inhibits the growth of influenza A PR/8/34 (PR8) virus (H1N1 subtype) in Madin-Darby canine kidney cells. The vital fluorescence microscopic study with acridine orange showed that 1-h treatment with (+)-catechin inhibited the acidification of ELS in a concentration-dependent manner (1.0-10.0 mM). Moreover, the growth of PR8 virus was inhibited markedly when the cells were treated with (+)-catechin (1.25-10.0 mM) for 1 h immediately after infection, or treated within as little as 5 to 10 min after infection. Conversely, virus growth resumed within 3 h concomitantly with the reappearance of acidified ELS after removal of (+)-catechin. Similar to EHext, (+)-catechin inhibited both the acidification of ELS and the influenza virus growth. It suggests that (+)-catechin is one of the active components in EHext.

L84 ANSWER 19 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001335565 EMBASE
TITLE: A melanosome-associated monoclonal antibody J1 recognizes luminal membrane of prelysosomes common to biogenesis of melanosomes and lysosomes.
AUTHOR: Shinoda K.; Wada I.; Jin H.-Y.; Jimbow K.

CORPORATE SOURCE: K. Jimbow, Department of Dermatology, Sapporo Medical Univ.
Sch. Medicine, South 1, West 16, Chuo-ku, Sapporo 060-8543,
Japan. jimbow@sapmed.ac.jp
SOURCE: Cell Structure and Function, (2001) 26/3 (169-177).
Refs: 23
ISSN: 0386-7196 CODEN: CSFUDY
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Melanogenesis cascade may be directly or indirectly linked to the dynamics of endosome-lysosome biogenesis. This study aims to identify how and to what extent the endosome-lysosome system is involved in melanosome biogenesis, by utilizing a novel melanogenesis marker, J1, which we identified in the process of developing monoclonal antibodies (MoAbs) against human melanosomes. The antigenic epitope of MoAb J1 was expressed by all of the melanotic and nonmelanotic cells examined. It was expressed primarily by granular structures located in regions proximal to the Golgi complex. Most of MoAb J1 positive granules were co-stained with melanogenic markers, tyrosinase or tyrosinase-related protein (TRP-1). The epitope of MoAb J1 was also co-expressed by most, but not all, of LGP85 (a lysosomal marker) positive granules in both melanoma and non-melanoma cells, indicating that MoAb J1 recognizes a subset of lysosomal vesicles. MoAb J1 did not, however, react with vesicles with late/early (syntaxin 8/EEA1) endosomal markers. Further examination using fluorophore-labeled pepstatin, a marker of lysosomal luminal content, confirmed that MoAb J1 specifically recognizes the luminal surface of lysosomes. These results indicate that MoAb J1 possesses an antigen epitope that is expressed in the luminal component of prelysosomal granules which are involved in the biogenesis cascade common to both melanosomes and lysosomes. We suggest that tyrosinase family protein, tyrosinase and TRP-1 are transported to melanosomes from TGN via these prelysosomal granules after being transiently transported to late endosomes.

L84 ANSWER 20 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000093133 EMBASE
TITLE: Effect of cationic liposomes on intracellular trafficking and efficacy of antisense oligonucleotides in mouse peritoneal macrophages.
AUTHOR: Takagi T.; Hashiguchi M.; Hiramatsu T.; Yamashita F.; Takakura Y.; Hashida M.
CORPORATE SOURCE: M. Hashida, Department of Drug Delivery Research, Grad. School Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan. hashidam@pharm.kyoto-u.ac.jp
SOURCE: Journal of Drug Targeting, (2000) 7/5 (363-371).
Refs: 33
ISSN: 1061-186X CODEN: JDTAEH
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have investigated the intracellular fate and antisense effect of oligonucleotide/cationic liposome complexes using phosphorothioate oligonucleotides (S-Oligo) targeted to inducible nitric oxide synthase in mouse peritoneal macrophages. Confocal laser microscopic analysis revealed that, after application of fluorescein isothiocyanate (FITC)-labeled

S-Oligo alone, the intracellular localization of fluorescence exhibited a punctate pattern in the cytoplasm, suggesting that the oligonucleotides were mainly confined to the **endosomal** and/or **lysosomal** compartments. In the case of complexation with Lipofectin and DMRIE-C liposomes, cellular uptake of FITC-S-Oligo was not greatly enhanced and the fluorescence localization in the cells was similar to that of FITC-S-Oligo alone. LipofectAMINE slightly enhanced cellular uptake of FITC-S-Oligo; however, the intracellular localization profile of FITC-S-Oligo remained largely unchanged. The antisense effect was slightly enhanced by LipofectAMINE under only very limited experimental conditions. It was concluded that cationic liposomes are not a potential carrier for S-Oligo in peritoneal macrophages because of their inability to promote the release of S-Oligo from the endosomal compartments to the cytosol over a non-toxic concentration range.

L84 ANSWER 21 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999144420 EMBASE

TITLE: Tamoxifen inhibits acidification in cells independent of the estrogen receptor.

AUTHOR: Altan N.; Chen Y.; Schindler M.; Simon S.M.

CORPORATE SOURCE: S.M. Simon, Laboratory of Cellular Biophysics, Rockefeller University, 1230 York Avenue, New York, NY 10021, United States. simon@rockvax.rockefeller.edu

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (13 Apr 1999) 96/8 (4432-4437). Refs: 57

ISSN: 0027-8424 CODEN: PNASA6

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Tamoxifen has been reported to have numerous physiological effects that are independent of the estrogen receptor, including sensitization of resistant tumor cells to many chemotherapeutic agents. Drug-resistant cells sequester weak base chemotherapeutics in acidic organelles away from their sites of action in the cytosol and nucleus. This work reports that tamoxifen causes redistribution of weak base chemotherapeutics from acidic organelles to the nucleus in drug-resistant cells. Agents that disrupt organelle acidification (e.g., monensin, bafilomycin A1) cause a similar redistribution. Measurement of cellular pH in several cell lines reveals that tamoxifen inhibits acidification of **endosomes** and **lysosomes** without affecting cytoplasmic pH. Similar to monensin, tamoxifen decreased the rate of vesicular transport through the recycling and secretory pathways. Organellar acidification is required for many cellular functions, and its disruption could account for many of the side effects of tamoxifen.

L84 ANSWER 22 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998386460 EMBASE

TITLE: Effect of bafilomycin A1 and nocodazole on endocytic transport in HeLa cells: Implications for viral uncoating and infection.

AUTHOR: Bayer N.; Schober D.; Prchla E.; Murphy R.F.; Blaas D.; Fuchs R.

CORPORATE SOURCE: R. Fuchs, General/Experimental Pathology Dept., University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. rene.fuchs@akh-wien.ac.at

SOURCE: Journal of Virology, (1998) 72/12 (9645-9655). Refs: 74

ISSN: 0022-538X CODEN: JOVIAM

COUNTRY: United States

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Bafilomycin A1 (baf), a specific inhibitor of vacuolar proton ATPases, is commonly employed to demonstrate the requirement of low endosomal pH for viral uncoating. However, in certain cell types baf also affects the transport of endocytosed material from early to late endocytic compartments. To characterize the endocytic route in HeLa cells that are frequently used to study early events in viral infection, we used 35S-labeled human rhinovirus serotype 2 (HRV2) together with various fluid-phase markers. These virions are taken up via receptor-mediated endocytosis and undergo a conformational change to C-antigenic particles at a pH of <5.6, resulting in release of the genomic RNA and ultimately in infection (E. Prchla, E. Kuechler, D. Blaas, and R. Fuchs, J. Virol. 68:3713-3723, 1994). As revealed by fluorescence microscopy and subcellular fractionation of microsomes by free-flow electrophoresis (FFE), baf arrests the transport of all markers in early endosomes. In contrast, the microtubule-disrupting agent nocodazole was found to inhibit transport by accumulating marker in endosomal carrier vesicles (ECV), a compartment intermediate between early and late **endosomes**. Accordingly, **lysosomal** degradation of HRV2 was suppressed, whereas its conformational change and infectivity remained unaffected by this drug. Analysis of the subcellular distribution of HRV2 and fluid-phase markers in the presence of nocodazole by FFE revealed no difference from the control incubation in the absence of nocodazole. ECV and late endosomes thus have identical electrophoretic mobilities, and intraluminal pHs of <5.6 and allow uncoating of HRV2. As bafilomycin not only dissipates the low endosomal pH but also blocks transport from early to late endosomes in HeLa cells, its inhibitory effect on viral infection could in part also be attributed to trapping of virus in early endosomes which might lack components essential for uncoating. Consequently, inhibition of viral uncoating by bafilomycin cannot be taken to indicate a low pH requirement only.

L84 ANSWER 23 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998345873 EMBASE
TITLE: Involvement of caspase-like proteinases in apoptosis of neuronal PC12 cells and primary cultured microglia induced by 6-hydroxydopamine.
AUTHOR: Takai N.; Nakanishi H.; Tanabe K.; Nishioku T.; Sugiyama T.; Fujiwara M.; Yamamoto K.
CORPORATE SOURCE: Dr. H. Nakanishi, Department of Pharmacology, Faculty of Dentistry, Kyushu University, Fukuoka 812-8582, Japan. nakandeg@mbbox.nc.kyushu-u.ac.jp
SOURCE: Journal of Neuroscience Research, (15 Oct 1998) 54/2 (214-222).
Refs: 41
ISSN: 0360-4012 CODEN: JNREDK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Activation of proteolytic enzymes, including the caspase family of proteinases, is a feature characteristic of the apoptotic program. In the present study, we examined a potential role of intracellular proteinases in the death of neuronal PC12 and primary cultured rat microglial cells induced by 6-hydroxydopamine (6-OHDA). In both neuronal PC12 and microglial cells, 6-OHDA (10-200 .mu.M) induced apoptosis in a dose-dependent manner as judged by the DNA break. The 6-OHDA was ineffective in Bcl-2-overexpressing neuronal PC12 cells. Pretreatment of

these cells with two caspase inhibitors, acetyl- Try-Val-Ala-Asp-aldehyde and acetyl-Asp-Glu-Val-Asp-aldehyde, prevented the 6-OHDA-induced apoptosis. Pepstatin A and leupeptin, potent inhibitors of aspartic and cysteine proteinases, respectively, partly inhibited the apoptosis of microglia but not neuronal PC12 cells. In contrast, GBR12935, a dopamine uptake inhibitor, significantly inhibited the apoptotic death of neuronal PC12 cells but not microglia. These results suggest that mechanisms by which 6-OHDA induces apoptosis in these two cell types are distinct; 6-OHDA incorporated into neuronal PC12 cells and its metabolites may activate the caspase-like enzymes, whereas oxidative metabolites of the agent produced extracellularly may activate the caspase and the **endosomal/lysosomal** proteolytic systems in microglia.

L84 ANSWER 24 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998043116 EMBASE

TITLE: .alpha.-tocopherol supplementation of macrophages does not influence their ability to oxidize LDL.

AUTHOR: Baoutina A.; Dean R.T.; Jessup W.

CORPORATE SOURCE: A. Baoutina, Cell Biology Unit, Heart Research Institute, 145 Missenden Road, Camperdown, NSW 2050, Australia

SOURCE: Journal of Lipid Research, (1998) 39/1 (114-130).

Refs: 57

ISSN: 0022-2275 CODEN: JLPRAW

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We have investigated the effect of .alpha.-tocopherol-loading of mouse peritoneal macrophages and human monocytes on their ability to oxidize human low density lipoprotein (LDL). Mouse peritoneal macrophages incorporated .alpha.- tocopherol (.alpha.-TOH) from culture medium supplemented with the vitamin in a time- and concentration-dependent manner. Subcellular fractionation by density gradient ultracentrifugation showed that the distribution of incorporated .alpha.-TOH within the cell was similar to that of free cholesterol. Most (.simeq.88%) of .alpha.-TOH partitioned into the membrane fractions (plasma membrane .simeq.41%, mitochondria and **lysosomes** .simeq.26%, and **endosomes** plus endoplasmic reticulum .simeq.21%). Cellular .alpha.-TOH was stable for at least 24 h in serum- or LDL-free media whether permissive (Ham's F-10) or non-permissive (Dulbecco's minimum essential medium, DMEM) for LDL oxidation. When incubated with LDL in DMEM, .alpha.-TOH-preloaded cells transferred small amounts of .alpha.-TOH (approximately 1 nmol/mg LDL protein after 9 h) to the lipoprotein. However, enrichment of the cells with .alpha.-TOH did not change the kinetics of oxidation of either normal or TOH-depleted LDL in Ham's F-10 medium compared with non- loaded cells, as assessed by .alpha.-TOH consumption, cholesteryl ester degradation, and cholesteryl ester hydroperoxide and 7-ketocholesterol accumulation. Nor did it alter superoxide release by the cells or their ability to reduce extracellular copper(II). Similar to mouse macrophages, enrichment of human monocytes with .alpha.-TOH did not change the kinetics of cell-mediated LDL oxidation. B We conclude that elevated cellular levels of .alpha.-TOH in mouse peritoneal macrophages and in human monocytes do not affect their ability to oxidize LDL lipids in vitro. This suggests that either cell- mediated oxidation of LDL under the conditions of this study is not dependent on cell-derived radical species or that cellular .alpha.-TOH is unable to affect their formation.

L84 ANSWER 25 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96127672 EMBASE

DOCUMENT NUMBER: 1996127672

TITLE: An ultrastructure study of the in vitro effects of L-leucine methyl ester and ammonium chloride on Trypanosoma

cruzi epimastigotes.
AUTHOR: Bogitsh B.J.; Ribeiro-Rodrigues R.; Carter C.E.
CORPORATE SOURCE: Department of Biology, Vanderbilt University, Nashville, TN
37235, United States
SOURCE: Parasitology Research, (1996) 82/4 (285-290).
ISSN: 0044-3255 CODEN: PARREZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Trypanosoma cruzi epimastigotes were subjected to the lysosomotropic agents L-leucine methyl ester and ammonium chloride to determine their effects on the ultrastructure of the parasite. The lysosomotropic agents applied to epimastigotes caused a time-dependent alteration in the morphology of the cells marked by a 5-fold increase in the number of lysosomes. Continued exposure to ammonium chloride caused slight disruption of the reservosomes. The amino acid ester, however, while causing the parasite to swell after prolonged exposure (e.g., 24 h), had little effect on the reservosomes, the kinetoplast, or even the mitochondrion. A specific inhibitor of cysteine proteinases provided some protection for lysosomes from the effects of the amino acid ester. Although it is agreed that reservosomes are similar to **endosomes**, no **lysosomal** fusion with the reservosomes was observed. Acid phosphatase activity was observed only in lysosomes.

L84 ANSWER 26 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 94102020 EMBASE
DOCUMENT NUMBER: 1994102020
TITLE: Cell death induced by peroxidized low-density lipoprotein:
Endopepsis.
AUTHOR: Fossel E.T.; Zanella C.L.; Fletcher J.G.; Hui K.K.S.
CORPORATE SOURCE: Department of Radiology, Beth Israel Hospital, 330
Brookline Ave., Boston, MA 02215, United States
SOURCE: Cancer Research, (1994) 54/5 (1240-1248).
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Peroxidized low-density lipoprotein (p-LDL) has been previously demonstrated to be preferentially cytotoxic to certain malignant cells compared to normal cells of the same type. We present evidence that p-LDL is at least partially taken up through the LDL receptor and that it becomes localized in lysosomes. The integrity of lysosomes of p-LDL-treated cells is compromised, and leakage of their contents into the cytosol occurs. This leakage occurs early and precedes mitochondrial dysfunction. Brefeldin A inhibits this leakage, perhaps by interfering with the traffic between **endosomes** and **lysosomes**. Electron micrographs taken at various times suggest a mechanism of cell death which resembles certain aspects of the broad definition of apoptosis. However, we suggest that the cell death observed following p-LDL-induced release of lysosomal contents is essentially unique, with released lysosomal enzymes degrading the cell from within. We suggest that this process should be described as endopepsis.

L84 ANSWER 27 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 94049700 EMBASE
DOCUMENT NUMBER: 1994049700

TITLE: Pathways of intracellular trafficking and release of ferritin by the liver in vivo: The effect of chloroquine and cytochalasin D.
AUTHOR: Ramm G.A.; Powell L.W.; Halliday J.W.
CORPORATE SOURCE: Liver Unit, Bancroft Centre, Queensland Inst. of Medical Research, 300 Herston Road, Brisbane, QLD 4029, Australia
SOURCE: Hepatology, (1994) 19/2 (504-513).
ISSN: 0270-9139 CODEN: HPTLD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have previously shown that the clearance of exogenous ferritin and the release of endogenous ferritin into both serum and bile are altered by the microtubular inhibitor colchicine. In this study we further examined the role of the **lysosome-endosome** pathway in ferritin metabolism. We examined the effect of the lysosomotropic agent chloroquine and the microtubular inhibitor cytochalasin D on the uptake and release of ferritin by normal and iron-loaded rats under basal conditions and in the presence of an exogenous tissue ferritin load. Either chloroquine (50 mg/kg body wt) or cytochalasin D (0.9 .mu.g/100 gm body wt/min) was administered to normal and iron-loaded rats at zero time. Rats were also infused with either saline solution or rat liver ferritin containing a trace amount of 125I-ferritin. The clearance of 125I-ferritin from the circulation was not affected by chloroquine or cytochalasin D either in normal or in iron-loaded rats; however, both chloroquine and cytochalasin D decreased the serum ferritin concentration in normal rats to 39% .+- 9% and 22% .+- 7% of the baseline serum ferritin levels, respectively, implying that both drugs inhibited the release of endogenous ferritin in normal rats. In iron-loaded rats both chloroquine and cytochalasin D decreased the biliary ferritin concentration to 11% .+- 1% and 37% .+- 4% of the baseline ferritin levels, respectively, and the 125I protein-bound counts per minute in the bile to 50% of the control result. This finding is consistent with an inhibitory effect of both drugs on the biliary excretion of endogenous ferritin and the intracellular transport of exogenous ferritin, respectively. In the presence of an exogenous tissue ferritin load, there was no detectable inhibitory effect of either drug on the biliary excretion of either endogenous or exogenous ferritin. These results provide the following evidence: (a) the receptor-mediated endocytosis of ferritin is not dependent on functioning lysosomes or microfilaments; (b) the release of endogenous ferritin into the serum of normal rats and the bile of iron-loaded rats is a chloroquine-sensitive, microfilament-dependent process; (c) the biliary excretion of trace amounts of exogenous ferritin is dependent on both chloroquine-sensitive vesicles and microfilaments; and (d) increased levels of exogenous ferritin are excreted directly into the bile by way of a second microfilament-independent, chloroquine-insensitive pathway. This study provides support for a physiological mechanism for the release of ferritin from the liver.

L84 ANSWER 28 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 93346256 EMBASE
DOCUMENT NUMBER: 1993346256
TITLE: Effect of morphine on mesangial immunoglobulin G aggregate kinetics.
AUTHOR: Singhal P.C.; Pan C.Q.; Gibbons N.; Valderrama E.
CORPORATE SOURCE: Nephrology Div., Long Island Jewish Medical Center, New Hyde Park, NY 11042, United States
SOURCE: American Journal of Physiology - Cell Physiology, (1993) 265/5 34-5 (C1211-C1219).
ISSN: 0002-9513 CODEN: AJPCDD
COUNTRY: United States

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Because mesangial expansion is considered a precursor of focal glomerulosclerosis, we studied whether morphine can cause mesangial expansion. We used radiolabeled human immunoglobulin G aggregates (125I-ahIgG) to study mesangial kinetics in control and experimental (morphine-treated) rats. Control and experimental rats were administered 125I-ahIgG by tail vein. Serum levels of 125I-ahIgG and uptake of 125I-ahIgG by liver, spleen, and mesangium were determined at 4, 8, 12, 24, and 36 h after 125I-ahIgG administration. Mesangial 125I-ahIgG levels were higher ($P < 0.05$) at 4 h and at later periods in morphine-treated vs. control rats. Naloxone, an opioid antagonist, did not attenuate the morphine-induced mesangial accumulation of 125I-ahIgG. The mean uptake of IgG aggregates was lower in the liver and spleen of morphine-treated rats at 36 h ($P < 0.05$). In both in vivo and in vitro experiments, ultrastructural studies showed accumulation of IgG-coated gold particles in vesicles, **endosomes**, and **lysosomes**. Morphine may have increased the accumulation of 125I-ahIgG in the glomeruli either by increasing the delivery of macromolecules into the mesangium or by altering the exit of macromolecules from the mesangium.

L84 ANSWER 29 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 93286801 EMBASE

DOCUMENT NUMBER: 1993286801

TITLE: The mouse brown (b) locus protein has dopachrome tautomerase activity and is located in lysosomes in transfected fibroblasts.

AUTHOR: Winder A.J.; Wittbjør A.; Rosengren E.; Rorsman H.

CORPORATE SOURCE: Glaxo Group Research Ltd, Greenford Road, Greenford, Middlesex UB6 0HE, United Kingdom

SOURCE: Journal of Cell Science, (1993) 106/1 (153-166).
ISSN: 0021-9533 CODEN: JNCSAI

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Many genes mapping to pigmentation loci are involved in the regulation of melanin synthesis in the mouse. The brown (b) locus controls black/brown coat coloration, and its product has significant homology to the key melanogenic enzyme tyrosinase. This has led to suggestions that the b-protein is itself a melanogenic enzyme. In order to investigate its function, we have established lines of mouse fibroblasts stably expressing the b-protein by co-transfection of a b-protein expression vector and a plasmid conferring resistance to the antibiotic G418. The b-protein synthesised by these cells has the expected molecular mass of 75 kDa and reacts with three different anti-b-protein antibodies. We were unable to confirm previous reports that the b-protein has tyrosinase or catalase activity, but detected stereospecific dopachrome tautomerase activity in b-protein-expressing fibroblasts. This dopachrome tautomerase binds to Concanavalin A-Sepharose, and the major product of its action on L-dopachrome is 5,6-dihydroxyindole-2-carboxylic acid. Since this activity is not present in untransfected cells we conclude that the b-protein has dopachrome tautomerase activity. Fibroblasts do not contain melanosomes, the specialised organelles in which the b-protein is located in melanocytes. Nevertheless, indirect immunofluorescence localisation of the b-protein in transfected fibroblasts produces a distinctive pattern of intense juxtanuclear staining combined with punctate cytoplasmic staining.

Double-labelling shows co-localisation of the b-protein with the late endosomal/lysosomal markers .beta.-glucuronidase and LAMP-1, both in transfected fibroblasts and in mouse melanoma cells. These findings are consistent with the hypothesis that melanosomes are closely related to lysosomes.

L84 ANSWER 30 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 92191473 EMBASE

DOCUMENT NUMBER: 1992191473

TITLE: Sequestration of organic cations by acidified hepatic endocytic vesicles and implications for biliary excretion.

AUTHOR: Van Dyke R.W.; Faber E.D.; Meijer D.K.F.

CORPORATE SOURCE: Gastroenterology Division, 6520 MSRB-I, Michigan University Medical Center, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-0682, United States

SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1992) 261/1 (1-11).

ISSN: 0022-3565 CODEN: JPETAB

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB A number of cationic amine drugs that are taken up by liver and excreted into bile may accumulate in acidified intracellular organelles such as **lysosomes** and **endosomes**. These studies were undertaken to assess directly the uptake and accumulation of three types of model organic cationic amines by endocytic vesicles, and the role of vesicle acidification in this process. Uptake of tubocurarine (TC), vecuronium and tributylmethylammonium (TBuMA) by purified rat liver multivesicular bodies (MVB) (prelysosomal endocytic vesicles) was dependent upon MgATP, time and drug concentration. After 60 min, 52 to 81% of MVB cation content was dependent upon vesicle acidification (due to an electrogenic proton pump), but not upon an interior positive vesicle membrane potential. Nineteen to 42% of MVB cation content appeared due to binding to MVB membranes or to internal lipoproteins. Vesicle-to-medium ATP-dependent apparent concentration ratios for these three cations were 3.3 to 51. MVB uptake of these cations resembled uptake of methylamine, a tertiary amine known to distribute across organellar membranes according to pH gradients. By contrast, MVB uptake of the lipophilic quaternary amine methyldepropine was not dependent upon MgATP or on development of MVB pH or membrane potential gradients. In further studies, TC, vecuronium and TBuMA were rapidly taken up by the isolated perfused rat liver and excreted in bile. Exposure to 250 .mu.M primaquin (which partially alkalinized acidic **endosomes** and **lysosomes**) reduced accumulation of [3H]vecuronium in a lysosomal fraction by 23%, decreased perfusate disappearance of TC and TBuMA, but not of vecuronium, and decreased biliary appearance of all three cations. These studies suggest that acidified intracellular organelles sequester certain organic cationic drugs, possibly via a drug/proton antiporter, and/or diffusion followed by intravesicular protonation and trapping of tertiary amines. However, attempts at partial displacement of these drugs, accomplished through partial vesicle alkalinization by primaquin, decreased excretion of TC, vecuronium and TBuMA, perhaps reflecting the small functional size of the displaceable organellar drug compartment and/or competition between primaquin and the organic cations for membrane transport processes.

L84 ANSWER 31 OF 34 WPIDS (C) 2002 THOMSON DERWENT

ACCESSION NUMBER: 2002-674932 [72] WPIDS

DOC. NO. CPI: C2002-190137

TITLE: Ocular pigment epithelial cells, useful for treating e.g. macular degeneration by implantation, are transformed

with large-capacity adenoviral vector.
 DERWENT CLASS: B04 D16
 INVENTOR(S): KOCHANNEK, S; SCHRAERMEYER, U; THUMANN, G
 PATENT ASSIGNEE(S): (KOCH-I) KOCHANNEK S; (SCHR-I) SCHRAERMEYER U
 COUNTRY COUNT: 98
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002066620	A2	20020829	(200272)*	GE	59
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW					
DE 10108412	A1	20021010	(200274)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002066620	A2	WO 2002-EP1853	20020221
DE 10108412	A1	DE 2001-10108412	20010221

PRIORITY APPLN. INFO: US 2001-270746P 20010222; DE 2001-10108412
20010221

AB WO 200266620 A UPAB: 20021108
 NOVELTY - Pigment epithelial cells (A) of the eye that contain vector DNA (I) of an adenoviral vector (AdV) with large DNA capacity, are new.
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
 (1) (A) in the form of a compact association ('cell sheet');
 (2) culture system comprising at least one (A) and a feeder layer;
 (3) method for preparing (A) that contain (I);
 (4) method for preparing the association of (a); and
 (5) method for preparing (A) by culturing in the system of (b).
 ACTIVITY - Ophthalmological; antidiabetic; antiparkinsonian.
 Iris pigment cells, transformed with an AdV that expresses pigment epithelial cell-derived factor, were transplanted into Royal College of Surgeons rats, then 2 months later examined microscopically for photoreceptor nuclei. The mean number of nuclei was 4.4, compare 2.2 for non-transformed cells, and the rhodopsin-positive area was 54000 micron², compared with zero, indicating protection against photoreceptor degradation.
 MECHANISM OF ACTION - Protein or cell replacement; non-transformed (A) produce **melanin** and this had an antioxidant action (by chelating metal ions and thus preventing formation of oxygen free radicals).
 USE - (A) Are used for treatment (by implantation) of:
 (a) eye diseases, especially age-related macular degeneration, glaucoma, diabetic retinopathy and genetic disorders of the pigmentary epithelium; and
 (b) nervous system diseases, specifically Parkinson's disease.
 They can also be used diagnostically (no details).
 ADVANTAGE - AdV provides long-term, stable expression (over at least 4 weeks), of incorporated genes, and very efficient in vitro transduction.
 Dwg.0/2

L84 ANSWER 32 OF 34 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2001-102933 [11] WPIDS
 DOC. NO. NON-CPI: N2001-076383
 DOC. NO. CPI: C2001-030192

TITLE: Screening for compounds that modulate **melanogenesis**, useful in cosmetic and therapeutic alteration of pigmentation, from their effect of tyrosinase cellular localization.

DERWENT CLASS: B04 D16 S03

INVENTOR(S): MANGA, P; ORLOW, S J; HALL, A

PATENT ASSIGNEE(S): (UYNY) UNIV NEW YORK STATE; (HALL-I) HALL A; (MANG-I) MANGA P; (ORLO-I) ORLOW S J

COUNTRY COUNT: 28

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001001131	A1	20010104	(200111)*	EN	67
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA HU IL JP KR NZ ZA					
AU 2000052419	A	20010131	(200124)		
US 2002034772	A1	20020321	(200224)		
EP 1190248	A1	20020327	(200229)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
HU 2002001647	A2	20020828	(200264)		
KR 2002042541	A	20020605	(200277)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001001131	A1	WO 2000-IB861	20000627
AU 2000052419	A	AU 2000-52419	20000627
US 2002034772	A1 Provisional CIP of	US 1999-141563P	19990629
		US 2000-599487	20000623
		US 2001-827428	20010406
EP 1190248	A1	EP 2000-937135	20000627
		WO 2000-IB861	20000627
HU 2002001647	A2	WO 2000-IB861	20000627
		HU 2002-1647	20000627
KR 2002042541	A	KR 2001-716792	20011228

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000052419	A Based on	WO 200101131
EP 1190248	A1 Based on	WO 200101131
HU 2002001647	A2 Based on	WO 200101131

PRIORITY APPLN. INFO: US 1999-141563P 19990629; US 2000-599487 20000623; US 2001-827428 20010406

AB WO 200101131 A UPAB: 20021105

NOVELTY - Screening for compounds (A) that inhibit **melanogenesis** comprises treating cells that express a tyrosinase (I) gene with test compound and determining cellular localization of (I). Any change in localization caused by the test compound indicates a candidate inhibitor.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) similar method for screening compounds (A1) that increase **melanogenesis** by detecting a change, caused by a test compound, in the amount of (I) secreted from the cells; and

(b) screening for compounds (B) that affect the function of P protein (Pp).

ACTIVITY - None given.

MECHANISM OF ACTION - (A) cause mislocation of (I), increasing its secretion from cells or directing it to non-melanosomal vesicles. P

protein is required for proper cellular localization (to the melanosomal membranes) of (I) and other melanosomal proteins, and is needed for full activity of (I) and **melanogenesis**.

No relevant data given.

USE - (A) And compounds that increase **melanogenesis**, are potentially useful as pharmaceutical or cosmetic agents for reducing/increasing synthesis of **melanin** in humans and animals, e.g. to alter **pigmentation** of **skin** and hair. Similar methods are also used to identify modulators of P protein, and these can be used similarly to alter **pigmentation** of hair, **skin** and eyes.

Dwg.0/12

L84 ANSWER 33 OF 34 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2000-171087 [15] WPIDS
 DOC. NO. NON-CPI: N2000-127161
 DOC. NO. CPI: C2000-053206
 TITLE: In vivo introduction of a therapeutic agent into **skin** or muscle **cells** of a subject using a pulsed electric field.
 DERWENT CLASS: B04 B07 P34 S05
 INVENTOR(S): DEV, N B; HOFMANN, G A; NOLAN, E; RABUSSAY, D; TONNESSEN, A; WIDERA, G; ZHANG, L; RABUSSAY, D P
 PATENT ASSIGNEE(S): (GENE-N) GENETRONICS INC; (DEVN-I) DEV N B; (HOFM-I) HOFMANN G A; (NOLA-I) NOLAN E; (RABU-I) RABUSSAY D P; (TONN-I) TONNESSEN A; (WIDE-I) WIDERA G; (ZHAN-I) ZHANG L
 COUNTRY COUNT: 23
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000002621	A1	20000120	(200015)*	EN	77
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP US					
AU 9949883	A	20000201	(200028)		
EP 1100579	A1	20010523	(200130)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 2002099323	A1	20020725	(200254)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000002621	A1	WO 1999-US15755	19990713
AU 9949883	A	AU 1999-49883	19990713
EP 1100579	A1	EP 1999-933937	19990713
		WO 1999-US15755	19990713
US 2002099323	A1 Provisional	US 1998-92544P	19980713
	Provisional	US 1998-109324P	19981120
	Provisional	US 1999-126058P	19990325
		US 1999-352809	19990713

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9949883	A Based on	WO 200002621
EP 1100579	A1 Based on	WO 200002621

PRIORITY APPLN. INFO: US 1999-126058P 19990325; US 1998-92544P 19980713; US 1998-109324P 19981120; US 1999-352809 19990713

AB WO 200002621 A UPAB: 20000323

NOVELTY - In vivo introduction of a therapeutic agent into **skin** or muscle **cells** of a subject, comprises applying a pulsed electric field to the skin or muscle simultaneously with the application of the therapeutic agent to the **skin** or muscles **cells** to introduce the therapeutic agent to the **skin** or muscle **cells**.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a method for inducing an immune response in a subject, comprising applying a pulsed electric field to **skin** or muscle **cells** simultaneously with the application of an immune response inducing agent to the **skin** or muscle **cells**, causing introduction of the agent into the cells, inducing an immune response;

(2) a micropatch electrode for use with electroporation apparatus, comprising a substantially planar array of patch elements comprising two sets of electrodes, each set of electrodes contain two electrically insulated electrodes so that when a different electric potential is applied to the electrodes a voltage is produced between them;

(3) an electrode kit for use in conjunction with electroporation therapy comprising

(a) a micropatch electrode (110) having a planar array of patch elements; and

(b) an injection needle (120), optionally comprising one or more holes disposed along its length and proximal to the needle tip (122);

(4) a method for the therapeutic application of electroporation to **skin** or muscles **cells** or a subject for introducing topically applied molecules into the cells, comprising

(a) providing an array electrodes, at least one electrodes having a needle configuration for penetrating tissue;

(b) inserting the needle electrode into the selected tissue;

(c) positioning a second electrode of the array of electrodes in conductive relation to the selected tissue; and

(d) applying pulses of high amplitude electric signals to the electrodes, proportionate to the distance between the electrodes, for electroporation of the tissue;

(5) an electrode for use with an electroporation apparatus, comprising an array of paired electrode needles and at least one injection needle, where a potential difference applied to the electrodes creates a voltage between them;

(6) an electrode for use with an electroporation apparatus, comprising a suction generating device comprising a ring electrode which, when contacted with the skin and suction is applied, causes the skin to be pulled up around the injection needle, piercing the skin, a potential difference applied between the ring-shaped electrode and injection needle electrode creates a voltage;

(7) a needle electrode for use with an electroporation apparatus, comprising an injection needle and a paired electrically conducting wires in the hollow core and protruding from the tip, the wires have an insulated and an uninsulated portion, the uninsulated portion being at the tip end;

(8) a needle electrode for use with an electroporation apparatus having a substance releasing material around a portion of its length;

(9) a needle electrode for use with an electroporation apparatus, comprising

(a) a hollow central core;

(b) at least four holes along its length, comprising two paired holes, which comprise a proximal and a distal hole relative to the needle tip; and

(c) a pair of electrically conducting wires having an electrically insulated portion and an exposed conducting portion, the wires are located in the hollow core apart from an electrically exposed part which runs outside of the needle from the distal paired hole to the proximal paired hole; and

(10) a needle electrode for use with an electroporation apparatus, comprising electrically conducting needles disposed within a depth guide, the tip extends for a predetermined distance beyond the depth guide.

USE - The electroporation device is used for in vivo introduction of a therapeutic agent into **skin** or muscle **cells** of a subject (claimed).

ADVANTAGE - The electroporation for skin and muscle-directed gene therapy eliminates of the risk of generating novel disease-causing agents, delivers DNA molecules much larger than can be package into a virus, and has no immune responses or toxic side effects caused by non-DNA material, e.g. viral proteins or cationic lipids. The DNA enters the cell through a non-**endosomal** pathway, diminishing the rate of DNA degradation. The method is simple, highly reproducible and cost-effective.

DESCRIPTION OF DRAWING(S) - The figure shows a micropatch electroporation applicator that has a micropatch member and an injection needle.

Electroporation applicator 100

Micropatch member 110

Injection needle 120

Conduit 121

Needle tip 122

Dwg.1/22

L84 ANSWER 34 OF 34 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 1996-424612 [42] WPIDS
 CROSS REFERENCE: 1996-361914 [36]; 1997-076787 [07]; 1997-086593 [08];
 1997-296853 [25]
 DOC. NO. CPI: C1996-133741
 TITLE: Topical compsn. for stimulating **melanogenesis**
 in the skin - contains lyso-somotropic agent, e.g.
 ammonium chloride, that increases **melanin**
 levels in melanocyte(s), and opt. a methyl-xanthine to
 produce a streak-free tan.
 DERWENT CLASS: B02 D21
 INVENTOR(S): FULLER, B B
 PATENT ASSIGNEE(S): (OKLA) UNIV OKLAHOMA STATE
 COUNTRY COUNT: 1
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5554359	A	19960910	(199642)*		18

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5554359	A	Cont of	US 1989-451420 19891215
		CIP of	US 1992-943998 19920911
			US 1994-251072 19940531

PRIORITY APPLN. INFO: US 1994-251072 19940531; US 1989-451420
 19891215; US 1992-943998 19920911

AB US 5554359 A UPAB: 19970709

Compsn. (A) for stimulating **melanogenesis** in human **skin**
cells comprises a **lysosomotropic** agent (I) that
 increases the levels of **melanin** in human melanocytes, and a
 topical carrier able to deliver (I) to melanocytes in vivo.

Also new are similar compsns. that additionally contain a
 methylxanthine (II) able to increase **melanin** content in
 melanocytes.

USE - The compsns. promote tanning without potentially harmful

exposure to radiation and increases protection against UV light.

ADVANTAGE - Since the compsn. is not a dye, it produces a streak-free tan.

Dwg.6/8

=> fil embase; d que 15

FILE 'EMBASE' ENTERED AT 16:05:56 ON 17 DEC 2002
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FILE COVERS 1974 TO 12 Dec 2002 (20021212/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L1 1161 SEA FILE=EMBASE ABB=ON MELANOGENESIS/CT
L2 3533 SEA FILE=EMBASE ABB=ON P(A)PROTEIN OR GLYCINE CLEAVAGE
SYSTEM/CT
L3 82 SEA FILE=EMBASE ABB=ON ADENOSINE TRIPHOSPHATASE/CT AND ENZYME
INHIBITOR/CT
L4 713 SEA FILE=EMBASE ABB=ON ADENOSINE TRIPHOSPHATASE INHIBITOR/CT
~~L5 6 SEA FILE=EMBASE ABB=ON L1 AND (L2 OR L3 OR L4)~~

=> fil medl; d que 128

FILE 'MEDLINE' ENTERED AT 16:05:57 ON 17 DEC 2002

FILE LAST UPDATED: 14 DEC 2002 (20021214/UP). FILE COVERS 1958 TO DATE.

On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See <http://www.nlm.nih.gov/mesh/summ2003.html> for a description on changes.

If you received SDI results from MEDLINE on October 8, 2002, these may have included old POPLINE data and in some cases duplicate abstracts. For further information on this situation, please visit NLM at: http://www.nlm.nih.gov/pubs/techbull/so02/so02_popline.html

To correct this problem, CAS will remove the POPLINE records from the MEDLINE file and process the SDI run dated October 8, 2002 again.

Customers who received SDI results via email or hard copy prints on October 8, 2002 will not be charged for this SDI run. If you received your update online and displayed answers, you may request a credit by contacting the CAS Help Desk at 1-800-848-6533 in North America or 614-447-3698 worldwide, or via email to help@cas.org

This file contains CAS Registry Numbers for easy and accurate substance identification.

L22 3530 SEA FILE=MEDLINE ABB=ON PROTEIN#(A)P
L23 3024 SEA FILE=MEDLINE ABB=ON ADENOSINETRIPHOSPHATASE/CT(L)AI/CT
L24 1166 SEA FILE=MEDLINE ABB=ON MELANOGENESIS
L25 5427 SEA FILE=MEDLINE ABB=ON MELANINS/CT
L26 1287 SEA FILE=MEDLINE ABB=ON SKIN+NT/CT AND PIGMENTATION+NT/CT
L27 2677 SEA FILE=MEDLINE ABB=ON SKIN PIGMENTATION/CT
~~L28 7 SEA FILE=MEDLINE ABB=ON (L22 OR L23) AND (L24 OR L25 OR L26
OR L27)~~

=> fil wpids; d que 133

FILE 'WPIDS' ENTERED AT 16:05:59 ON 17 DEC 2002

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FILE LAST UPDATED: 16 DEC 2002 <20021216/UP>
MOST RECENT DERWENT UPDATE: 200281 <200281/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY >>>

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
SEE <http://www.derwent.com/dwpi/updates/dwpicov/index.html> <<<

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

L29 205 SEA FILE=WPIDS ABB=ON PROTEIN#(A)P
L30 672 SEA FILE=WPIDS ABB=ON ATPASE# OR ADENOSINETRIPHOSPHATASE OR
ADENOSINE(W) (TRI PHOSPHATASE OR TRIPHOSPHATASE)
L31 278 SEA FILE=WPIDS ABB=ON L30(3A)INHIBIT?
L32 2421 SEA FILE=WPIDS ABB=ON MELANIN# OR MELANOGENESIS OR SKIN(5A)PIG
MENT?
~~L33 2 SEA FILE=WPIDS ABB=ON (L29 OR L31) AND L32~~

=> fil capl; d que l43

FILE 'CAPLUS' ENTERED AT 16:06:02 ON 17 DEC 2002
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FILE COVERS 1907 - 17 Dec 2002 VOL 137 ISS 25
FILE LAST UPDATED: 16 Dec 2002 (20021216/ED)

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CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

L34 5052 SEA FILE=CAPLUS ABB=ON MELANINS/CT
L35 796 SEA FILE=CAPLUS ABB=ON MELANOGENESIS/OBI
L36 2596 SEA FILE=CAPLUS ABB=ON SKIN(L)PIGMENT?/OBI
L37 1245 SEA FILE=CAPLUS ABB=ON P(A)PROTEIN#/OBI
~~L38 1 SEA FILE=REGISTRY ABB=ON "P PROTEINS"/CN~~

L39 1 SEA FILE=REGISTRY ABB=ON ATPASE/CN
 L40 1440 SEA FILE=CAPLUS ABB=ON L38 OR L37
 L41 61012 SEA FILE=CAPLUS ABB=ON L39 OR (ATPASE# OR ADENOSINETRIPHOSPHAT
 ASE OR ADENOSINE(W) (TRI PHOSPHATASE))/OBI
 L42 8285 SEA FILE=CAPLUS ABB=ON L41(L)INHIBIT?/OBI
~~L43 7 SEA FILE=CAPLUS ABB=ON (L34 OR L35 OR L36) AND (L40 OR L42)~~

~~=> dup rem 128,143,15,133~~

FILE 'MEDLINE' ENTERED AT 16:06:05 ON 17 DEC 2002

FILE 'CAPLUS' ENTERED AT 16:06:05 ON 17 DEC 2002
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 PROCESSING COMPLETED FOR L28
 PROCESSING COMPLETED FOR L43
 PROCESSING COMPLETED FOR L5
 PROCESSING COMPLETED FOR L33

~~L85 18 DUP REM L28 L43 L5 L33 (4 DUPLICATES REMOVED)~~
 ANSWERS '1-7' FROM FILE MEDLINE
 ANSWERS '8-14' FROM FILE CAPLUS
 ANSWERS '15-17' FROM FILE EMBASE
 ANSWER '18' FROM FILE WPIDS

~~=> d-ibib-ab-hitrn 1-18~~ fil hom

L85 ANSWER 1 OF 18 MEDLINE DUPLICATE 2
 ACCESSION NUMBER: 2001555718 MEDLINE
 DOCUMENT NUMBER: 21488331 PubMed ID: 11602344
 TITLE: Human pigmentation genes: identification, structure and
 consequences of polymorphic variation.
 AUTHOR: Sturm R A; Teasdale R D; Box N F
 CORPORATE SOURCE: Centre for Functional and Applied Genomics, Institute for
 Molecular Bioscience, University of Queensland, Brisbane,
 QLD 4072, Australia.. r.sturm@imb.uq.edu.au
 SOURCE: GENE, (2001 Oct 17) 277 (1-2) 49-62. Ref: 78
 Journal code: 7706761. ISSN: 0378-1119.
 PUB. COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200112
 ENTRY DATE: Entered STN: 20011017
 Last Updated on STN: 20020122
 Entered Medline: 20011213
 AB The synthesis of the visible pigment melanin by the melanocyte cell is the
 basis of the human pigmentary system, those genes directing the formation,
 transport and distribution of the specialised melanosome organelle in
 which melanin accumulates can legitimately be called pigmentation genes.
 The genes involved in this process have been identified through
 comparative genomic studies of mouse coat colour mutations and by the
 molecular characterisation of human hypopigmentary genetic diseases such
 as OCA1 and OCA2. The melanocyte responds to the peptide hormones
 alpha-MSH or ACTH through the MC1R G-protein coupled receptor to stimulate

melanin production through induced maturation or switching of melanin type. The pheomelanosome, containing the key enzyme of the pathway tyrosinase, produces light red/yellowish melanin, whereas the eumelanosome produces darker melanins via induction of additional TYRP1, TYRP2, SILV enzymes, and the **P-protein**. Intramelanosomal pH governed by the **P-protein** may act as a critical determinant of tyrosinase enzyme activity to control the initial step in melanin synthesis or TYRP complex formation to facilitate **melanogenesis** and melanosomal maturation. The search for genetic variation in these candidate human pigmentation genes in various human populations has revealed high levels of polymorphism in the MC1R locus, with over 30 variant alleles so far identified. Functional correlation of MC1R alleles with skin and hair colour provides evidence that this receptor molecule is a principle component underlying normal human pigment variation.

L85 ANSWER 2 OF 18 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001412103 MEDLINE
DOCUMENT NUMBER: 21354456 PubMed ID: 11461115
TITLE: Melanosomal pH controls rate of **melanogenesis**, eumelanin/pheomelanin ratio and melanosome maturation in melanocytes and melanoma cells.
AUTHOR: Ancans J; Tobin D J; Hoogduijn M J; Smit N P; Wakamatsu K; Thody A J
CORPORATE SOURCE: Department of Biomedical Sciences, University of Bradford, Bradford, BD7 1DP, United Kingdom.
SOURCE: EXPERIMENTAL CELL RESEARCH, (2001 Aug 1) 268 (1) 26-35. Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809
AB The skin pigment melanin is produced in melanocytes in highly specialized organelles known as melanosomes. Melanosomes are related to the organelles of the endosomal/lysosomal pathway and can have a low internal pH. In the present study we have shown that melanin synthesis in human pigment cell lysates is maximal at pH 6.8. We therefore investigated the role of intramelanosomal pH as a possible control mechanism for **melanogenesis**. To do this we examined the effect of neutralizing melanosomal pH on tyrosinase activity and **melanogenesis** in 11 human melanocyte cultures and in 3 melanoma lines. All melanocyte cultures (9 of 9) from Caucasian skin as well as two melanoma cell lines with comparable melanogenic activity showed rapid (within 24 h) increases in **melanogenesis** in response to neutralization of melanosomal pH. Chemical analysis of total melanin indicated a preferential increase in eumelanin production. Electron microscopy revealed an accumulation of melanin and increased maturation of melanosomes in response to pH neutralization. In summary, our findings show that: (i) near neutral melanosomal pH is optimal for human tyrosinase activity and **melanogenesis**; (ii) melanin production in Caucasian melanocytes is suppressed by low melanosomal pH; (iii) the ratio of eumelanin/pheomelanin production and maturation rate of melanosomes can be regulated by melanosomal pH. We conclude that melanosomal pH is an essential factor which regulates multiple stages of melanin production. Furthermore, since we have recently identified that pink locus product (**P protein**) mediates neutralization of melanosomal pH, we propose that **P protein** is a key control point for skin pigmentation. We would further propose that the wide variations in both constitutive and facultative skin pigmentation seen in the human

population could be associated with the high degree of P-locus polymorphism.
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L85 ANSWER 3 OF 18 MEDLINE
ACCESSION NUMBER: 2002289227 MEDLINE
DOCUMENT NUMBER: 22025544 PubMed ID: 12028586
TITLE: The etiology of oculocutaneous albinism (OCA) type II: the pink protein modulates the processing and transport of tyrosinase.
AUTHOR: Toyofuku Kazutomo; Valencia Julio C; Kushimoto Tsuneto; Costin Gertrude-E; Virador Victoria M; Vieira Wilfred D; Ferrans Victor J; Hearing Vincent J
CORPORATE SOURCE: Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.
SOURCE: PIGMENT CELL RESEARCH, (2002 Jun) 15 (3) 217-24.
Journal code: 8800247. ISSN: 0893-5785.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020528
Last Updated on STN: 20021031
Entered Medline: 20021030

AB Oculocutaneous albinism (OCA) is caused by reduced or deficient melanin pigmentation in the skin, hair, and eyes. OCA has different phenotypes resulting from mutations in distinct pigmentation genes involved in **melanogenesis**. OCA type 2 (OCA2), the most common form of OCA, is an autosomal recessive disorder caused by mutations in the P gene, the function(s) of which is controversial. In order to elucidate the mechanism(s) involved in OCA2, our group used several antibodies specific for various melanosomal proteins (tyrosinase, Tyrp1, Dct, Pmel17 and HMB45), including a specific set of polyclonal antibodies against the **p protein**. We used confocal immunohistochemistry to compare the processing and distribution of those melanosomal proteins in wild type (melan-a) and in p mutant (melan-pl) melanocytes. Our results indicate that the melanin content of melan-pl melanocytes was less than 50% that of wild type melan-a melanocytes. In contrast, the tyrosinase activities were similar in extracts of wild type and p mutant melanocytes. Confocal microscopy studies and pulse-chase analyses showed altered processing and sorting of tyrosinase, which is released from melan-pl cells to the medium. Processing and sorting of Tyrp1 was also altered to some extent. However, Dct and Pmel17 expression and subcellular localization were similar in melan-a and in melan-pl melanocytes. In melan-a cells, the **p protein** showed mainly a perinuclear pattern with some staining in the cytoplasm where some co-localization with HMB45 antibody was observed. These findings suggest that the **p protein** plays a major role in modulating the intracellular transport of tyrosinase and a minor role for Tyrp1, but is not critically involved in the transport of Dct and Pmel17. This study provides a basis to understand the relationship of the **p protein** with tyrosinase function and melanin synthesis, and also provides a rational approach to unveil the consequences of P gene mutations in the pathogenesis of OCA2.

L85 ANSWER 4 OF 18 MEDLINE
ACCESSION NUMBER: 2001554941 MEDLINE
DOCUMENT NUMBER: 21487268 PubMed ID: 11601658
TITLE: Inverse correlation between pink-eyed dilution protein expression and induction of **melanogenesis** by bafilomycin A1.
AUTHOR: Manga P; Orlow S J

CORPORATE SOURCE: The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, NY 10016, USA.
CONTRACT NUMBER: EY10223 (NEI)
SOURCE: PIGMENT CELL RESEARCH, (2001 Oct) 14 (5) 362-7.
Journal code: 8800247. ISSN: 0893-5785.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20011017
Last Updated on STN: 20020419
Entered Medline: 20020418

AB The pink-eyed dilution **protein (p)** plays a pivotal role in the synthesis of eumelanin. In its absence, critical melanosomal proteins fail to traffic to the melanosome. Pink-eyed dilution gene (P) mutations are the most common cause of tyrosinase-positive oculocutaneous albinism worldwide. Thus, reports that bafilomycin A1 was able to induce synthesis of melanin in tyrosinase-positive melanomas led us to test the drug on p-null murine melanocytes. We found that in melanocytes lacking p, bafilomycin A1 was able to induce melanin synthesis. These cells, once transfected with an expression vector encoding an epitope-tagged p transcript, failed to respond to the drug. The increase in melanin synthesis is accompanied by a reduction in tyrosinase protein cleavage and secretion with subsequent accumulation within the melanocyte. Bafilomycin A1 has also been reported to induce pigmentation of normal Caucasian melanocytes. Based on these data we hypothesize that p may serve as a key control point at which ethnic skin color variation is determined.

L85 ANSWER 5 OF 18 MEDLINE
ACCESSION NUMBER: 2001211758 MEDLINE
DOCUMENT NUMBER: 20494768 PubMed ID: 11041370
TITLE: Molecular bases of congenital hypopigmentary disorders in humans and oculocutaneous albinism 1 in Japan..
AUTHOR: Tomita Y; Miyamura Y; Kono M; Nakamura R; Matsunaga J
CORPORATE SOURCE: Department of Dermatology, Nagoya University School of Medicine, Japan.. tomita@med.nagoya-u.ac.jp
SOURCE: PIGMENT CELL RESEARCH, (2000) 13 Suppl 8 130-4.
Journal code: 8800247. ISSN: 0893-5785.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: (LECTURES)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB The molecular bases of various types of congenital hypopigmentary disorders have been clarified in the past 10 years. Homozygous gene mutations of enzymes functional in **melanogenesis** such as tyrosinase, **P protein** and DHICA oxidase, result in oculocutaneous albinism (OCA) 1, OCA 2, and OCA 3, respectively. The genes responsible for Hermansky-Pudlak syndrome (HPS) and Chediak-Higashi syndrome (CHS) have also recently been isolated and cloned. The transcription factor paired box 3 (PAX3) works at the promoter region of the microphthalmia-associated transcription factor (MITF) gene, and the MITF transcription factor orders the expression of c-kit, which encodes the receptor for stem-cell factor, which in turn stimulates melanoblast migration from the neural tube to the skin in the embryo. Heterozygous mutations of PAX3, MITF, or c-kit genes induce Waardenburg syndrome (WS) 1/3, WS 2 or Piebaldism, respectively. A defect of endothelin-3 or the endothelin-B receptor produces WS 4. In our examination of 26 OCA 1 patients in Japan, all were found to have homozygous or heterozygous

tyrosinase gene mutations at codons 77 or 310. Therefore, mutations at codons 77 and 310 are the major ones in Japanese patients with OCA 1. An autosomal dominant pigmentary disease of dyschromatosis symmetrica hereditaria (DSH) is well known in Japan, and is characterized by a mixture of hypo- and hyper-pigmented macules of various sizes on the backs of the hands and feet. The disease gene and its chromosomal localization have not been identified yet. Our trial of linkage analysis and positional cloning to determine the disease gene is presented.

L85 ANSWER 6 OF 18 MEDLINE
ACCESSION NUMBER: 1999036995 MEDLINE
DOCUMENT NUMBER: 99036995 PubMed ID: 9819560
TITLE: Human pigmentation genetics: the difference is only skin deep.
AUTHOR: Sturm R A; Box N F; Ramsay M
CORPORATE SOURCE: Centre for Molecular and Cellular Biology, University of Queensland, Brisbane, Australia.. r.sturm@mailbox.uq.edu.au
SOURCE: BIOESSAYS, (1998 Sep) 20 (9) 712-21. Ref: 84
Journal code: 8510851. ISSN: 0265-9247.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20021019
Entered Medline: 19990104

AB There is no doubt that visual impressions of body form and color are important in the interactions within and between human communities. Remarkably, it is the levels of just one chemically inert and stable visual pigment known as melanin that is responsible for producing all shades of humankind. Major human genes involved in its formation have been identified largely using a comparative genomics approach and through the molecular analysis of the pigmentary process that occurs within the melanocyte. Three classes of genes have been examined for their contribution to normal human color variation through the production of hypopigmented phenotypes or by genetic association with skin type and hair color. The MSH cell surface receptor and the melanosomal **P-protein** are the two most obvious candidate genes influencing variation in pigmentation phenotype, and may do so by regulating the levels and activities of the melanogenic enzymes tyrosinase, TRP-1 and TRP-2.

L85 ANSWER 7 OF 18 MEDLINE
ACCESSION NUMBER: 97313757 MEDLINE
DOCUMENT NUMBER: 97313757 PubMed ID: 9170158
TITLE: Molecular basis of congenital hypopigmentary disorders in humans: a review.
AUTHOR: Boissy R E; Nordlund J J
CORPORATE SOURCE: Department of Dermatology, University of Cincinnati College of Medicine, Ohio 45267-0592, USA.
SOURCE: PIGMENT CELL RESEARCH, (1997 Feb-Apr) 10 (1-2) 12-24. Ref: 111
Journal code: 8800247. ISSN: 0893-5785.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707

ENTRY DATE: Entered STN: 19970812
Last Updated on STN: 19970812
Entered Medline: 19970729

AB Many specific gene products are sequentially made and utilized by the melanocyte as it emigrates from its embryonic origin, migrates into specific target sites, synthesizes melanin(s) within a specialized organelle, transfers pigment granules to neighboring cells, and responds to various exogenous cues. A mutation in many of the respective encoding genes can disrupt this process of **melanogenesis** and can result in hypopigmentary disorders. Following are examples highlighting this scenario. A subset of neural crest derived cells emigrate from the dorsal surface of the neural tube, become committed to the melanoblast lineage, and are targeted along the dorsal lateral pathway. The specific transcription factors PAX3 and MITF (microphthalmia transcription factor) appear to play a regulatory role in early embryonic development of the pigment system and in associated diseases (the Waardenburg syndromes). During the subsequent development and commitment of the melanoblast, concomitant expression of the receptors for fibroblasts growth factor (FGFR2), endothelin-B (EDNRB), and steel factor (cKIT) also appears essential for the continued survival of migrating melanoblasts. Lack or dysfunction of these receptors result in Apert syndrome, Hirschsprung syndrome and piebaldism, respectively. Once the melanocyte resides in its target tissue, a plethora of melanocyte specific enzymes and structural proteins are coordinately expressed to form the melanosome and to convert tyrosine to melanin within it. Mutations in the genes encoding these proteins results in a family of congenital hypopigmentary diseases called oculocutaneous albinism (OCA). The tyrosinase gene family of proteins (tyrosinase, TRP1, and TRP2) regulate the type of eumelanin synthesized and mutations affecting them result in OCA1, OCA3, and slaty (in the murine system), respectively. The **P protein**, with 12 transmembrane domains localized to the melanosome, has no assigned function as of yet but is responsible for OCA2 when dysfunctional. There are other genetically based syndromes, phenotypically resembling albinism, in which the synthesis of pigmented melanosomes, as well as specialized organelles of other cell types, is compromised. The Hermansky-Pudlak syndrome (HPS) and the Chediak-Higashi syndrome (CHS) are two such disorders. Eventually, the functional melanocyte must be maintained in the tissue throughout life. In some cases it is lost either normally or prematurely. White hair results in the absence of melanocytes repopulating the germinative hair follicle during subsequent anagen stages. Vitiligo, in contrast, results from the destruction and removal of the melanocyte in the epidermis and mucous membranes.

L85 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2001:12721 CAPLUS
DOCUMENT NUMBER: 134:66123
TITLE: Screening methods for compounds that affect
melanogenesis and **P protein**
function
INVENTOR(S): Orlow, Seth J.; Manga, Prashiela
PATENT ASSIGNEE(S): New York University, USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001001131	A1	20010104	WO 2000-IB861	20000627
W: AU, CA, HU, IL, JP, KR, NZ, ZA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,				

PT, SE
EP 1190248 A1 20020327 EP 2000-937135 20000627
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI
PRIORITY APPLN. INFO.: US 1999-141563P P 19990629
WO 2000-IB861 W 20000627
AB Methods of screening for compds. that affect melanogenesis and the
function of P protein in organisms, cells, or cell-free systems are
provided. The invention further relates to the pharmacol. and cosmetic
uses of such compds. to reduce or increase the synthesis of melanin in
animal and human melanocytes and melanocyte-derived cells.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L85 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4
ACCESSION NUMBER: 2000:505834 CAPLUS
DOCUMENT NUMBER: 133:250110
TITLE: Activation of **melanogenesis** by vacuolar type
H⁺-ATPase inhibitors in
amelanotic, tyrosinase positive human and mouse
melanoma cells
AUTHOR(S): Ancans, J.; Thody, A. J.
CORPORATE SOURCE: Department of Biomedical Sciences, University of
Bradford, Bradford, BD7 1DP, UK
SOURCE: FEBS Letters (2000), 478(1,2), 57-60
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, the authors describe the activation of melanogenesis by
selective vacuolar type H⁺-ATPase inhibitors (bafilomycin A1 and
concanamycin A) in amelanotic human and mouse melanoma cells which express
tyrosinase but show no melanogenesis. Addn. of the inhibitors activated
tyrosinase within 4 h, and by 24 h the cells contained measurable amts. of
melanin. These effects were not inhibited by cycloheximide (2 .mu.g/mL)
which is consistent with a post-translational mechanism of activation.
The authors' findings suggest that melanosomal pH could be an important
and dynamic factor in the control of melanogenesis in mammalian cells.

IT 9000-83-3, ATPase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(hydrogen ion-translocating; **melanogenesis** activation by
vacuolar type H⁺-ATPase inhibitors in amelanotic,
tyrosinase pos. human and mouse melanoma cells)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L85 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:221159 CAPLUS
DOCUMENT NUMBER: 136:257280
TITLE: Methods and compositions that affect
melanogenesis
INVENTOR(S): Orlow, Seth J.; Hall, Andrea; Manga, Prashiela
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 63 pp., Cont.-in-part of U. S.
Ser. No. 599,487.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

US 2002034772 A1 20020321 US 2001-827428 20010406
WO 2002098347 A2 20021212 WO 2002-US11067 20020408
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, TR

PRIORITY APPLN. INFO.:

US 1999-141563P P 19990629
US 2000-599487 A2 20000623
US 2001-827428 A 20010406

AB The invention provides methods of screening for compds. that affect melanogenesis and the function of P protein in organisms, cells, or cell-free systems. The invention further relates to pharmacol. and cosmetic uses of methods of inhibiting melanogenesis, methods of activating melanogenesis, and compds. and pharmacol. compns. useful for the inhibition or activation of melanogenesis and, therefore, for lightening or darkening the pigmentation of cells and tissue, i.e., skin.

IT 9000-83-3, ATPase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibition**; methods and compns. that affect
melanogenesis)

L85 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:121389 CAPLUS

DOCUMENT NUMBER: 136:306060

TITLE: Increase of pro-opiomelanocortin mRNA prior to tyrosinase, tyrosinase-related protein 1, dopachrome tautomerase, Pmel-17/gp100, and **P-protein** mRNA in human skin after ultraviolet B irradiation

AUTHOR(S): Suzuki, Itaru; Kato, Tomomi; Motokawa, Tomonori; Tomita, Yasushi; Nakamura, Eriko; Katagiri, Takayuki
CORPORATE SOURCE: R&D Department of Dermatological Sciences, POLA Chemical Industries, Inc., Yokohama, 560, Japan
SOURCE: Journal of Investigative Dermatology (2002), 118(1), 73-78

CODEN: JIDEAE; ISSN: 0022-202X

PUBLISHER: Blackwell Science, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In UV-induced tanning, the protein levels of various gene products crit. for pigmentation (including tyrosinase and tyrosinase-related protein-1) are increased in response to UV B irradsn., but changes in mRNA levels of these factors have not been investigated in vivo. We have established an in situ hybridization technique to investigate mRNA levels of pro-opiomelanocortin, tyrosinase, tyrosinase-related protein-1, dopachrome tautomerase, P-protein, Pmel-17/gp100, and microphthalmia-assocd. transcription factor, and have analyzed the changes in mRNA levels in the UV B-exposed skin in vivo. The right or left forearm of each volunteer was irradiated with UV B, and skin biopsies were obtained at 2 and 5 d postirradn. MRNA level of proopiomelanocortin was increased 2 d after UV B irradsn., and returned to a near-basal level after 5 d, whereas the mRNA levels of tyrosinase, tyrosinase-related protein-1, dopachrome tautomerase, P-protein, and Pmel-17/gp100 showed some or no increase at 2 d, but were significantly increased 5 d after UV B irradsn. Microphthalmia-assocd. transcription factor mRNA was slightly increased on days 2 and 5 after UV B irradsn. Our results suggest that the mechanism of the tanning response of human skin may involve the transcriptional regulation of certain pigmentary genes, and that pro-opiomelanocortin-

derived melanocortins such as .alpha.-MSH and adrenocorticotrophic hormone may play a part in regulating these genes in vivo.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L85 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:481707 CAPLUS

DOCUMENT NUMBER: 136:181101

TITLE: Interaction between the melanocortin-1 receptor and P genes contributes to inter-individual variation in **skin pigmentation** phenotypes in a Tibetan population

AUTHOR(S): Akey, Joshua M.; Wang, Hong; Xiong, Momiao; Wu, Hong; Liu, Weida; Shriver, Mark D.; Jin, Li

CORPORATE SOURCE: School of Public Health, Human Genetics Center, University of Texas Texas-Houston, Houston, TX, 77030, USA

SOURCE: Human Genetics (2001), 108(6), 516-520
CODEN: HUGEDQ; ISSN: 0340-6717

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The melanocortin-1 receptor (MC1R) and P gene product are two important components of the human pigmentary system that have been shown to be assocd. with red hair/fair skin and cause type II oculocutaneous albinism, resp. However, their contribution to inter-individual variation at the population level is not well defined. To this end, we genotyped 3 single nucleotide polymorphisms (SNPs) in the MC1R gene (Arg67Gln, Gln163Arg, Val92Met) and 2 SNPs in the P gene (IVS13-15 and Gly780Gly) in 184 randomly ascertained Tibetan subjects, whose skin color was measured as a quant. trait by reflective spectroscopy. Single locus analyses failed to demonstrate an assocn. between any of the 5 SNPs and skin pigmentation. However, when an epistatic model was applied to the data, a significant gene-gene interaction was identified between Val92Met in MC1R and IVS13-15 in the P gene ($F=2.43$; $P=0.0105$). We also discuss the possible mechanisms of how gene interactions arise in signal transduction pathways.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L85 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:552369 CAPLUS

DOCUMENT NUMBER: 135:341767

TITLE: Melanosomal pH, pink locus protein and their roles in **melanogenesis**

AUTHOR(S): Ancans, Janis; Hoogduijn, Martin J.; Thody, Anthony J.

CORPORATE SOURCE: Department of Biomedical Sciences, University of Bradford, Bradford, UK

SOURCE: Journal of Investigative Dermatology (2001), 117(1), 158-159

CODEN: JIDEAE; ISSN: 0022-202X

PUBLISHER: Blackwell Science, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with refs. The role of P protein (pink locus protein) in regulation of melanosomal pH and in facilitation of tyrosinase activity is discussed.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L85 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:795993 CAPLUS

DOCUMENT NUMBER: 132:31743

TITLE: Gene probes used for genetic profiling in healthcare

screening and planning
 INVENTOR(S): Roberts, Gareth Wyn
 PATENT ASSIGNEE(S): Genostic Pharma Limited, UK
 SOURCE: PCT Int. Appl., 149 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964626	A2	19991216	WO 1999-GB1779	19990604
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9941586	A1	19991230	AU 1999-41586	19990604
AU 9941587	A1	19991230	AU 1999-41587	19990604
GB 2339200	A1	20000119	GB 1999-12914	19990604
GB 2339200	B2	20010912		
EP 1084273	A1	20010321	EP 1999-925207	19990604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:				
			GB 1998-12098	A 19980606
			GB 1998-28289	A 19981223
			GB 1998-16086	A 19980724
			GB 1998-16921	A 19980805
			GB 1998-17097	A 19980807
			GB 1998-17200	A 19980808
			GB 1998-17632	A 19980814
			GB 1998-17943	A 19980819
			WO 1999-GB1779	W 19990604
AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.				

L85 ANSWER 15 OF 18 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002217504 EMBASE

TITLE: Pink-eyed dilution protein controls the processing of tyrosinase.

AUTHOR: Chen K.; Manga P.; Orlow S.J.

CORPORATE SOURCE: S.J. Orlow, R. O. Perelman Dept. of Dermatology, New York Univ. School of Medicine, New York, NY 10016, United

SOURCE: States. seth.orlow@med.nyu.edu
Molecular Biology of the Cell, (2002) 13/6 (1953-1964).
Refs: 42
ISSN: 1059-1524 CODEN: MBCEEV

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The processing of tyrosinase, which catalyzes the limiting reaction in melanin synthesis, was investigated in melan-pl melanocytes, which are null at the p locus. Endoglycosidase H digestion showed that a significant fraction of tyrosinase was retained in the endoplasmic reticulum. This retention could be rescued either by transfection of melan-pl cells with an epitope-tagged wild-type p transcript or by treatment with either bafilomycin A1 or ammonium chloride. We found that the endoplasmic reticulum contains a significant amount of **p protein**, thus supporting a role for p within this compartment. Using immunofluorescence, we showed that most mature full-length tyrosinase in melan-pl cells was located in the perinuclear area near the Golgi, in contrast to its punctate melanosomal pattern in wild-type melanocytes. Expression of p in melan-pl cells restored tyrosinase to melanosomes. Triton X-114 phase separation revealed that an increased amount of tyrosinase was proteolyzed in melan-pl cells compared with wild-type melanocytes. The proteolyzed tyrosinase was no longer membrane bound, but remained enzymatically active and a large proportion was secreted into the culture medium of melan-pl cells. We conclude that p regulates posttranslational processing of tyrosinase, and hypopigmentation in melan-pl cells is the result of altered tyrosinase processing and trafficking.

L85 ANSWER 16 OF 18 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002093197 EMBASE

TITLE: Melanosomal pH, pink locus protein and their roles in melanogenesis [3].

AUTHOR: Brilliant M.; Gardner J.

CORPORATE SOURCE: M. Brilliant, Department of Pediatrics, Univ. of Arizona School of Medicine, Tucson, AZ, United States

SOURCE: Journal of Investigative Dermatology, (2001) 117/2 (386-387).
Refs: 20
ISSN: 0022-202X CODEN: JIDEAE

COUNTRY: United States

DOCUMENT TYPE: Journal; Letter

FILE SEGMENT: 002 Physiology
013 Dermatology and Venereology
029 Clinical Biochemistry

LANGUAGE: English

L85 ANSWER 17 OF 18 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96155938 EMBASE

DOCUMENT NUMBER: 1996155938

TITLE: Mutation in and lack of expression of tyrosinase-related protein-1 (TRP- 1) in melanocytes from an individual with brown oculocutaneous albinism: A new subtype of albinism classified as 'OCA3'.

AUTHOR: Boissy R.E.; Zhao H.; Oetting W.S.; Austin L.M.; Wildenberg S.C.; Boissy Y.L.; Zhao Y.; Sturm R.A.; Hearing V.J.; King R.A.; Nordlund J.J.

CORPORATE SOURCE: Department of Dermatology, University of Cincinnati, P. O. Box 670592, Cincinnati, OH 45267-0592, United States

SOURCE: American Journal of Human Genetics, (1996) 58/6 (1145-1156).

ISSN: 0002-9297 CODEN: AJHGAG
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 012 Ophthalmology
 013 Dermatology and Venereology
 022 Human Genetics
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB Most types of human oculocutaneous albinism (OCA) result from mutations in the gene for tyrosinase (OCA1) or the **P protein** (OCA2), although other types of OCA have been described but have not been mapped to specific loci. Melanocytes were cultured from an African-American with OCA, who exhibited the phenotype of Brown OCA, and his normal fraternal twin. Melanocytes cultured from the patient with OCA and the normal twin appeared brown versus black, respectively. Melanocytes from both the patient with OCA and the normal twin demonstrated equal amounts of NP-40-soluble melanin; however, melanocytes from the patient with OCA contained only 7% of the amount of insoluble melanin found from the normal twin. Tyrosinase-related protein-1 (TRP-1) was not detected in the OCA melanocytes by use of various anti-TRP-1 probes. Furthermore, transcripts for TRP-1 were absent in cultured OCA melanocytes. The affected twin was homozygous for a single-bp deletion in exon 6, removing an A in codon 368 and leading to a premature stop at codon 384. Tyrosine hydroxylase activity of the OCA melanocytes was comparable to controls when assayed in cell lysates but was only 30% of controls when assayed in intact cells. We conclude that this mutation of the human TRP-1 gene affects its interaction with tyrosinase, resulting in dysregulation of tyrosinase activity, promotes the synthesis of brown versus black melanin, and is responsible for a third genetic type of OCA in humans, which we classify as 'OCA3.'

L85 ANSWER 18 OF 18 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2001-483049 [52] WPIDS
 DOC. NO. CPI: C2001-144771
 TITLE: Monoleucine dependent basolateral sorting signal useful for modulating basolateral expression of basolaterally targeted transmembrane proteins, useful for treating cancer, atherosclerosis and psoriasis.
 DERWENT CLASS: B04 D16
 INVENTOR(S): IMHOF, B A; WEHRLE-HALLER, B M
 PATENT ASSIGNEE(S): (UYGE-N) UNIV GENEVE
 COUNTRY COUNT: 95
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001047950	A2	20010705	(200152)*	EN	82
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001025119	A	20010709	(200164)		
EP 1240196	A2	20020918	(200269)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001047950	A2	WO 2000-EP13141	20001222

AU 2001025119 A
EP 1240196 A2

AU 2001-25119 20001222
EP 2000-988804 20001222
WO 2000-EP13141 20001222

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001025119	A Based on	WO 200147950
EP 1240196	A2 Based on	WO 200147950

PRIORITY APPLN. INFO: WO 1999-CH624 19991223

AB WO 200147950 A UPAB: 20010914

NOVELTY - A monoleucine dependent basolateral sorting signal (I) (comprising the defined amino acid sequence (A1) given in the specification), is new.

DETAILED DESCRIPTION - A monoleucine dependent basolateral sorting signal (I) comprising amino acid sequence (A1):

X1h2X3h4L p5p6 (A1)

X1 = a polar amino acid residue or alanine;

h2 = any hydrophobic amino acid residue;

X3 = any amino acid residue;

h4 = any hydrophobic amino acid residue, except leucine and isoleucine;

L = a leucine residue; and

p5 and p6 = any polar amino acid residue.

INDEPENDENT CLAIMS are also included for the following:

(1) a peptide or protein (II) comprising (I), where the peptide or protein does not comprise full-length human, mouse, chicken, cat, dog, horse, cow, sheep, swine, quail, rat or salamander stem cell factor (SCF);

(2) an antibody (Ab) or its fragment, specifically recognizing (I) or (II);

(3) a nucleic acid molecule (III) comprising a sequence encoding (I) or (II), or their complements;

(4) a cell (IV) expressing (II) or (III);

(5) a method (M1) of obtaining basolateral expression of a transmembrane protein T containing (I), by expressing in a polarized cell, a nucleic acid encoding the protein;

(6) screening (M2) for identifying inhibitor of basolateral expression, by introducing into a polarized cell, a compound to be tested for an inhibitory property, detecting in the cell modification of basolateral expression of a reporter protein and emergence of apical expression for the reporter protein, and optionally recovering the identified inhibitor;

(7) inhibitors (V) of (I), capable of inhibiting basolateral expression of a protein containing (I), obtained from M2; and

(8) use of a composition (C) comprising (II), (III) or (V), for the manufacture of a medicament to modify the intercellular roles of SCF, and in cosmetology to reduce **skin pigmentation**.

ACTIVITY - Antiarteriosclerotic; cytostatic; antiallergic; osteopathic; hemostatic; antipsoriatic; dermatological.

MECHANISM OF ACTION - Modulator of basolateral expression of basolaterally targeted transmembrane protein (claimed); vaccine; gene therapy.

No supporting data given.

USE - (II) is useful for inhibiting basolateral expression of a transmembrane protein which is normally expressed specifically in the basolateral membrane of polarized cell, and for abolishing basolateral sorting of transmembrane proteins e.g., SCF, of type I or type II topology, bearing (I). (I) and (II) are useful for modulating basolateral expression of a basolaterally targeted transmembrane protein, by introducing (I) or (II) into a cell expressing P selected from Sertoli cells, keratinocytes, lung epithelial cells, kidney epithelial cells,

endothelial cells of skin, cells from respiratory and alimentary tract, from aorta and bone marrow, osteoblasts, thymic epithelial cells, ovary cells and neurons expressing SCF.

(I) and (II) are useful for modulating membrane retention of a transmembrane protein T, by introducing (I) or (II) into a cell expressing T selected from dermal fibroblasts, heart atrium, smooth muscle cells of the aorta, bone marrow stromal cells and Leydig cells. (C) is useful for the manufacture of a medicament to modify the intracellular roles of SCF, where the modification leads to a decrease of melanocyte proliferation, number of change in melanocyte localization, to reduce hyperpigmented skin lesion such as lentigo, lentigo senilis or neri, to treat melanoma cells, to eliminate melanocytes from UV damaged skin, to prevent allergic reactions mediated by mastocytes in the airway and alimentary tract, to treat monocytosis, leukemia or mastocytomas, to treat inhibition of spermatogenesis and oogenesis, to treat osteoporosis and hyperparathyroid bone, to treat hematopoietic precursor cell neoplasm, e.g., acute lymphoblastic leukemia (ALL), to treat psoriasis and atherosclerosis, and in cosmetology to reduce **skin pigmentation** (claimed).
Dwg.0/12

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